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**ARCHIVES**  
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CHICAGO 10

## ABNORMALITIES OF PIGMENTATION IN THE NEGRO

MEYER L. NIEDELMAN, M.D.

PHILADELPHIA

Although the study of the diseases of the skin in Negroes constitutes a most interesting specialty, this particular branch of dermatology has been largely neglected. The skin of persons of the Negro race differs from that of members of the white race not only in structure and physiology but in its reaction to trauma and infection. In the present article it is my intention to deal with only one phase of cutaneous disease in Negroes, namely abnormalities of pigmentation. For a better understanding of the latter, however, it will be necessary to consider briefly the history of the black race in the United States. In addition, certain personal experiences will be reported. These comprise a study of the incidence of mongolian blue spots in infants, together with the identification from pigmentation of white and Negro infants. Also, the collected literature on the abnormalities of pigmentation in Negroes will be reviewed.

## HISTORY OF THE NEGRO

The American Negro, according to Lewis<sup>1</sup> constitutes an alien element in the population of the United States, which has adapted itself in a most remarkable way to the climate and civilization of a country entirely different from that of its origin. It must be admitted that the Negroes in America have probably molded their life and habits to harmonize with their new environment much better than other races might have done had they been transplanted to tropical Africa. By intermarriage they have also absorbed some of

the qualities of the white race. It is not generally known that Negroes first came to America not as slaves but as companions of the Spanish explorers. It was not until 1619 that a Dutch vessel, making a chance landing at Jamestown, Va., brought the first slaves to America from Africa. Negroes were eventually imported from all parts of the African continent, but the chief source was the northwestern coast of Africa, where the darkest Negroes lived. After having lived in this country for many years, the Negroes grew lighter in color. It is possible that climate may have been a contributing factor, since it is well known that Europeans living in the tropics are known to grow darker.

## INHERITANCE OF COLOR OF THE SKIN

Children of families of mixed white and Negro blood show a wide variation in color, and in one family there may be one child almost white and another black. White parents have been known to bring forth children with distinct Negro characteristics due to unknown or denied Negro ancestors. This possibility and the uncertainty of its prediction are sources of dread to persons of mixed blood otherwise able to conceal their Negro ancestry. The children of mulatto-white crosses may be much darker or much lighter than either parent. The lightest child of a Negro-white cross may have more than twice as much black pigment as the average Caucasian, and the darkest, almost three-fifths as much as the darkest African. On the other hand, the lightest child of mulattoes may approximate very nearly the color of the ordinary brunette Caucasian, and the darkest may be about two-fifths as dark as the average African (fig. 1).

## MEASUREMENT OF PIGMENTATION

Much difficulty has been experienced by anthropologists in establishing the various colors encountered in human skins. These are not pure spectral colors but are composites of several color elements that defy analysis by mere inspection or by comparison with current color stand-

Part of a thesis submitted to the faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Master of Science in Dermatology and Syphilology.

From the Division of Dermatology and Syphilology, Graduate School of the University of Pennsylvania, F. D. Weidman, M.D., Vice Dean, the Department of Dermatology, Graduate School of the University of Pennsylvania; H. J. Smith, M.D., Chief, the Division of Dermatology and Syphilology, Temple University School of Medicine; C. S. Wright, M.D., Chief, and the Philadelphia General Hospital; J. V. Klauder, M.D., Chief.

<sup>1</sup> Lewis, I. H. *The Biology of the Negro*, Chicago University of Chicago Press, 1942.

known as the blue nevus of Jadassohn. According to Unna, it is only the great number of pigment granules in the skin of Negroes which permits some of this pigment to survive the pigment-reducing action of the prickly cells and to reach the surface undissolved. Normal Negro skin from the breasts contains abundant melanoblasts, many of which are dendritic.

Lewin and Peck<sup>6</sup> found that pigmented grafts caused extension of melanin into the surrounding

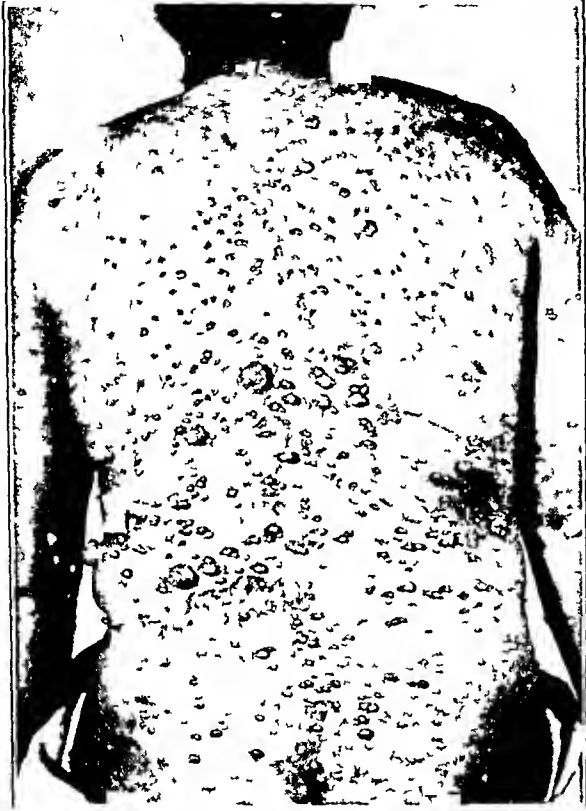


Fig 4—Von Recklinghausen's disease. A Negro aged 60, showing typical fibromatosis since the age of 8 years. A typical example of a café-au-lait spot is seen. The patient also had osseous and endocrine changes. His mentality was almost to the point of imbecility.

nonpigmented skin and that nonpigmented grafts in pigmented skin were invaded by pigment. They felt that these changes could not be explained by regeneration pigmentation alone. Becker followed the movement of melanin after transplantation of Negro skin into white skins and of white skin into Negro skin. He found that in each case the transplanted skin became the color of the host.

With regard to the time of development of pigment in Negroes, Thomson<sup>3</sup> was able to demonstrate pigment in the skin and hair follicles of a 5 month Negro fetus, and Adache, in fetuses of 6 to 7 months of age. The ears, the

roots of the nails and the scrotum darken earliest. As has been previously mentioned, the genitals of Negro infants are always darker than those of white infants. However, there are individual variations both in the amount of pigment at birth and in its rate of increase thereafter. According to Ziemann, complete pigmentation is attained three to four months after birth. Other writers have claimed that the process goes on to puberty or even old age.

Extracutaneous pigment is found in the mucous membranes of ectodermal origin. In Negroes melanin has been found in the mouth, pharynx, anal canal, superficial part of the lacteal ducts of the nipple and inner surface of the male and female prepuce. The areas of predilection in order of descending frequency are the surfaces of the gums, cheeks, hard palate, tongue and soft palate. The everted surfaces of the lips are always pigmented.

Monash<sup>7</sup> described the pigmented areas on the gums as flat, light brown and irregularly circular, varying from 1 to 4 mm in diameter and occupying approximately the center of the gingival surfaces. In darker subjects, the color is deeper and the patches confluent, forming a band along the center of the gum. On the dorsum of the tongue the pigmentation when present is asymmetric, and in the cheeks the median raphe is



Fig 5—Hyperpigmentation of papules in secondary syphilis.

pigmented. On the hard palate, either diffuse mottling or circular and elliptic areas may be

<sup>6</sup> Lewin, M. and Peck, S. M. Pigmented Studies in Skin Grafts on Experimental Animals, *J. Invest. Dermat.* 4: 453 (Dec.) 1941.

<sup>7</sup> Monash, S. Normal Pigmentation of the Oral Mucosa. *Arch. Dermat. & Syph.* 26: 139 (July) 1932.

present. Of all the Negroes examined by Monasli, only 5 per cent showed no pigmented areas in the mouth, and these would presumably have shown many melanoblasts on histologic examination. Certain colored persons are often seen to have pigmentation extending beyond the true skin into the mucous membrane of the mouth. These are the so-called "blue-gummed" people. Monasli examined 220 Negroes of varying degrees of pigmentation and of different ages and showed the existence of pigmented spots in the

the social and economic conditions of Negro life also play some part in determining the susceptibility of the race to certain disorders. The general ignorance, poverty and malnutrition of the neglected Negro element of the population all contribute to lend a special character to the incidence and manifestation of cutaneous diseases among them.

The dark color of Negro skin renders difficult the recognition of certain cutaneous disorders easily detected in white subjects by certain changes in color of the skin. Lowenthal has stated that "an entirely new set of visual memories must be built up." The changes in pigmentation have to be of a decided degree to be evident. In examining the patient, it is best to do so in bright daylight, in a room with white-washed walls. In order that the illumination of the lesions may be constant, the examiner should not move from his position, and the patient likewise should be asked to remain in one spot, only turning for inspection. Detection of slight degrees of erythema may be facilitated by placing a yellow glass before the eyes of the observer. A yellow filter is also said to be of aid in photographing erythematous macular lesions. Loewenthal<sup>4</sup> likewise recommended the use of a hand lens and of Unna's diascopic method in certain cases. It may be impossible to diagnose ecchymoses or purpuric spots unless the lesions can be recognized on the mucosa, except, of course, in light-skinned Negroes. A macule of depigmentation may vary in color from deep fawn to dead white. Papules tend to be lighter than the sur-



Fig 6—Steam burn. After prolonged treatment the areas healed with much scarring and depigmentation.

oral mucosa in 95 per cent (excluding newborn infants), which varied in appearance and location.

The conjunctivas are normally pigmented to a varying degree, the greatest concentration being in the scleral conjunctivas at the interpalpebral fissures and extending into the bulbar conjunctivas. Fisher (1905) found most pigment in the former site, in the immediate neighborhood of the scleras and extending deeply into the bulbar conjunctivas. The amount of pigment increases with age. Pigment is also found constantly in the meninges of Negroes, as in other races, and in the other extracutaneous sites mentioned elsewhere.

#### CLINICAL ASPECTS OF PIGMENTATION

The difference in anatomic structure and physiology of the skin of Negroes explains its different reaction to various cutaneous diseases. There is a difference not only in the incidence of many diseases but in their clinical and pathologic manifestations. There can be no doubt that



Fig 7—Depigmentation following prolonged pyoderma. A 17 year old Negress who had an ulcerative pyoderma of six months' duration, followed by depigmentation after healing.

rounding skin, and wheals are always lighter. Terry has discussed some of the clinical applications of fluorescence in relation to melanotic pigment. It seems that Negro skin does not normally fluoresce but can be made to fluoresce after exposure to actinic light for a time sufficient

to produce erythema in a Caucasian. However, normally, the negroid skin does appear different from the freckled areas in a Caucasian when viewed under filtered ultraviolet radiation.

#### CLINICAL CLASSIFICATION OF PIGMENTATION

##### I Physiologic—No increase or decrease in pigments

- 1 Stretching of the skin—there is less pigment per square unit of skin
- 2 Folding of the skin—there is more pigment per square unit of skin
- 3 Gray color due to scratching of the skin

##### II Pathologic

###### A Hyperpigmentation

- 1 Congenital
  - a Mongolian spot
  - b Blue nevus—Jadassohn
  - c Pigmentary moles and nevi (fig 2)
  - d Nevroid streaks (Andrews, 1933)
  - e Dermatosi papulosa nigra
- 2 Acquired
  - a Inflammatory diseases due to external causes—contact dermatitis, eczema (fig 2)
  - b Inflammatory diseases due to systemic conditions—Addison's disease, etc
  - c Extraneous introduction of pigment (tattoo)
  - d Drugs by mouth, injection or intranasally, i. e., arsenic, silver nitrate, phenolphthalein (fig 3)
  - e Exposure to sunlight
  - f Physical causes
- 3 Idiopathic—hyperpigmentation with no apparent cause (fig 4)

###### B Depigmentation

- 1 Congenital
  - a Albinism
    - (1) Complete
    - (2) Partial
  - b Xanthism
- 2 Acquired (partial list)
  - a Vitiligo
  - b Scleroderma and morphea
  - c Syphilis (fig 5)
  - d Yaws
  - e Leprosy
  - f Pinta
  - g Fungous diseases
  - h Virus diseases, i. e., herpes zoster
  - i Leukomelanoderma collis
  - j Lupus erythematosus
  - k Occupational dermatoses
  - l Progenic diseases and toxic dermatoses
  - m Molluscum contagiosum
  - n Pemphigus vulgaris
  - o Radium dermatitis
  - p Tuberculids
  - q Burns
  - r Alopecia areata
  - s Any inflammatory dermatosis in which the epidermis is destroyed (figs 6, 7, 8, 9)

Many conditions causing hyperpigmentation or depigmentation in Negroes have no such effect in persons of lighter-skinned races. Matas has suggested that the physiologic function of pig-



Fig 8—Multiple chancroids. Healed lesions showing depigmentation.



Fig 9—Lymphogranuloma venereum resembling granuloma inguinale. The Wassermann and the Ito-Reenstierna reactions were positive. There was depigmentation.

ment formation is under better control in highly pigmented subjects, with less tendency to uncon-



trolled growth, like that observed in melanoma. This malignant type of hyperpigmented tumor is usually fatal and occurs much more frequently in persons of white color. Furthermore, 70 per cent of these tumors develop in regions containing little pigment.

Fox<sup>8</sup> was the first to attempt a statistical comparison of cutaneous diseases affecting the white and the Negro races. He concluded that Negroes suffer less frequently and less severely from skin diseases than white persons, that mulattoes are more susceptible to skin diseases than full-blooded Negroes, the former being especially prone to chloasma, that Negroes are more subject to new growths of connective tissue origin and less so to neoplasms originating in epithelial structures, and, finally, that the Negro skin is less susceptible to external irritants.

All sorts of eruptions stimulate local increase of pigment as the result of inflammatory changes,

This so-called mongolian spot occurs as a bluish discoloration of irregular size and shape and is found most commonly over the sacrum, but it may also be found on the trunk, limbs or face. Noel found it present in 67 per cent of a series of newborn Negro infants. More than one such spot may be present. According to Loewenthal, the peculiar color is due to the filtering effect of the superimposed unpigmented upper third of the corium. As the epidermis grows darker, the bluish tinge fades, and in an adult Negro such a spot would be difficult to detect. The blue nevus of Jadassohn has been described by McCarthy as a persistent mongolian spot in a somewhat aberrant location.

I have examined 103 newborn Negro infants and found that 41 babies, or about 40 per cent, presented mongolian spots in the sacral area. Two infants had several spots on the buttocks, and 3 infants had spots on the thighs. I have



Fig 10—Vitiligo. A Negress aged 20, with unusual areas of vitiligo on the lips and an area behind the left ear. When first seen, she had a vitiliginous area of the right upper lid which responded to application of 10 per cent oil of bergamot in alcohol. At present this area is almost normal.

while conditions producing erosive lesions tend to cause depigmented spots.

Conditions seen less frequently in Negroes than in white subjects include carcinoma of the skin, leukoplakia, mycosis fungoides, Kaposi's sarcoma, pigmented nevi, xeroderma pigmentosum, psoriasis, roentgen dermatitis, occupational dermatoses, rosacea and seborrheic dermatitis. Eczema is also less common in Negroes than in white persons.

#### CONGENITAL HYPERPIGMENTATION

*Mongolian Spot*<sup>4</sup> During the fourth and fifth months of intrauterine life the presence of areas of dermal melanoblasts in the corium is normal. These cells exhibit a positive dopa reaction and in the Mongolian and Negro races persist until after birth, in many cases for years or even for life.

been unable to find any such spot on a white infant. As the infants become older and their skins darker, these areas become more difficult to find and outline. By the tenth day, it was impossible to distinguish them. This was true only of the dark-skinned babies.

#### ACQUIRED DEPIGMENTATION

*Vitiligo* Vitiligo is a disease characterized by the appearance of pigmentless patches. It is more common in Negroes than in white persons and is believed by some investigators to be a trophoneurosis. The pigment is destroyed in the patches and increased in the surrounding tissue. Numerous cases of vitiligo due to fungus infection have been reported. Thus, Iseki<sup>9</sup> reported 31 such cases in which the fungus was

<sup>8</sup> Fox, H. Observations on Skin Diseases in the Negro. *J. Cutan. Dis.* 26: 67 and 109, 1908.

<sup>9</sup> Iseki, K. Studie über die "Arterat," eine vitiliginöse Dermatose auf den Palau Inseln, *Acta dermat.* 23: 99, 1934.

grown in pure culture Fox<sup>10</sup> came to the definite conclusion that the high incidence of vitiligo in Yucatan was not due to a fungous infection Naegeli<sup>11</sup> reported on 4 patients with post-eczematous vitiligo, in all of whom the basal metabolic rate was increased This feature has been noted by numerous other investigators Touraine and Brizard<sup>12</sup> made a study of 53 cases in which the lesions were bilateral and symmetric They stated that in their opinion vitiligo is a neurodermatitis due to posterior radiculitis They expressed the belief that vitiligo is analogous to herpes zoster, which pathologically is known to be a posterior ganglionitis According to Constantino,<sup>13</sup> a consideration of the pathology of vitiligo must include not only biochemical factors but a study of the cutaneous circulation as well Roop<sup>14</sup> expressed the opinion that vitiligo is a result of absorption by the skin of certain decomposition products of sweat These products may be ammonia or ammonium carbonate and are believed to act as bleaching agents, attacking primarily the melanin of the pigmented cells In addition to reporting 4 cases of vitiligo definitely related to sweating, the author presented a case of its occurrence in a Negro child of 5 months, in which patches of vitiligo were found on removal of a diaper impregnated with decomposing urine and smelling strongly of ammonia

Pillsbury and Kulchar<sup>15</sup> reported 2 cases of vitiligo caused by the intravenous use of gold sodium thiosulfate They expressed the belief that the gold deposited in the depigmented areas failed to be reduced and eliminated and that a cumulative effect was thus produced which finally led to a gold dermatitis Sharlit<sup>16</sup> presented the case of a Negress with patches of vitiligo on her thighs These areas corresponded exactly to the rubber guards covering the garter clips on her girdle From this he decided that the leukoderma was due to an antioxidant in the rubber In an effort to produce repigmenta-

tion, he injected a suspension of tyrosinase intracutaneously into several areas in both patches At the time of his report it was too early to judge the end result

I recently had the opportunity of observing an interesting case of vitiligo of the lips of a young Negress, there was another depigmented patch behind the left ear An area on the right upper eyelid became repigmented after treatment with 10 per cent oil of bergamot in alcohol (fig 10)

*Lupus Erythematosus*—Considering the high susceptibility of the Negro race to pulmonary tuberculosis, it is remarkable that the incidence of lupus erythematosus among Negroes is generally conceded to be unusually low In 1918, Wise<sup>17</sup> stated that lupus erythematosus in Negroes was relatively uncommon in his experience In the discussion of this paper, Ochs drew



Fig 11—Lupus erythematosus A Negro, aged 50, showing atrophy and depigmentation of lesions of face Partial repigmentation followed treatment with a bismuth preparation, liver extract and nicotinic acid

attention to the fact that, although of rare occurrence in Negroes the disease when present appears to be more extensive than in white persons According to Gilchrist,<sup>18</sup> lupus erythematosus is rare in the Negro race, while lupus vulgaris is common Other writers reporting cases of lupus erythematosus in Negroes and emphasizing the rarity of the condition are Klauder,<sup>19</sup> Kirby-Smith,<sup>20</sup> Andrews,<sup>21</sup> and Cummer<sup>22</sup> Ac-

10 Fox, H White Pinta or Vitiligo in Yucatan, Arch Dermat & Syph 36 534 (Sept) 1937

11 Naegeli O Ueber postekzematoze echte Vitiligo, Schweiz med Wchnschr 66 1167 (Nov 21) 1936

12 Touraine A and Brizard, A La topographie radiculare du vitiligo Bull Soc franç de dermat et syph 42 505-515 (March) 1935

13 Constantino cited by Naegeli<sup>11</sup>

14 Roop W O Absorption of Decomposition Products of Sweat as an Etiologic Factor in Vitiligo, I M Soc New Jersey 31 339-343 (June) 1934

15 Pillsbury D M, and Kulchar, G V Gold Dermatitis Limited to Depigmented Skin, Arch Dermat & Syph 27 36 (Jan) 1933

16 Sharlit H Leukoderma Treated with Intracutaneous Injections of Tyrosinase Enzyme, Arch Dermat & Syph 48 438 (Oct) 1943

17 Wise, F Lupus Erythematosus, J Cutan Dis 37 354, 1919

18 Gilchrist, T C Lupus Erythematosus, Arch Dermat & Syph 1 597 (May) 1920

19 Klauder, J V Lupus Erythematosus, Arch Dermat & Syph 7 121 (Jan) 1923

20 Kirby-Smith, J L Erythematosus Lupus in Negro Youths Two Cases, J Florida M A 26 141 (Sept) 1939

According to Cummer, deep pigmentation affording a protection against the sun's rays is responsible for this rare incidence of the disease in Negroes. He collected from the literature 30 cases of lupus erythematosus in Negroes, and in New Orleans he found the incidence of this disease to be 3.5 per thousand among white patients with disorders of the skin.

I encountered 7 cases of lupus erythematosus in a large clinic for Negroes (fig. 11), 1 case of lupus vulgaris and 1 case each of lichen scrofulosus and papulonecrotic tuberculid.

---

21 Andrews, G. C. *Diseases of the Skin*, Philadelphia, W. B. Saunders Company, 1930.

22 Cummer, C. L. Etiology of Lupus Erythematosus. Occurrence in Negro, *Arch. Dermat. & Syph.* 33: 434 (March) 1936.

#### SUMMARY

From a study of part of the literature on the abnormalities of pigmentation in Negroes, I was led to make a personal study of certain aspects of the subject. These comprised an investigation of the incidence of mongolian blue spots in 103 newborn Negro infants, of whom 40 per cent presented such spots in the sacral areas. Also, an examination of several hundred newborn Negro infants revealed that their skin was unquestionably darker than that of white infants, and the most distinguishing feature was the dark, almost black, scrotum or vulva.

I encountered 7 cases of lupus erythematosus in a large clinic for Negroes, 1 case of lupus vulgaris and 1 case each of lichen scrofulosus and papulonecrotic tuberculid.

500 Central Medical Building



# ERYTHEMA MULTIFORME

## ITS RELATIONSHIP TO HERPES SIMPLEX

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LOS ANGELES

The purpose of this paper is to call attention to a probable etiologic relationship between herpes simplex and erythema multiforme. This relationship was first called to the attention of dermatologists by the Englishmen Forman and Whitwell ten years ago<sup>1</sup>. Since that time no confirmation of their observations has appeared in the American literature, and none of the leading American textbooks have even cited their work.

### HISTORICAL

Erythema multiforme, at least of the herpes iris type, was first described by Bateman,<sup>2</sup> in 1817. The first American communication was apparently that of H. D. Bulkley, of New York.<sup>3</sup> In the twelve years preceding 1846 he had observed 3 cases. It was sometime later that Hebra applied the term "erythema exsudativum multiforme". Still later Kaposi called it "erythema polymorphe".

### ETIOLOGY

The etiologic concepts of erythema multiforme have been those of association with definite infections. Thus it has been described as following smallpox vaccination<sup>4</sup> or occurring in the course of such diverse infections as typhoid fever,<sup>5</sup> diphtheria, syphilis,<sup>6</sup> tuberculosis,<sup>7</sup> chol-

era, pneumonia, leprosy, malaria and trypanosomiasis. The frequent association of erythema multiforme and menstruation has been noted by many observers, particularly Pollitzer.<sup>8</sup> The theory of focal infection as applied to erythema multiforme has received considerable support from the work of Guy.<sup>9</sup> In the investigation of 47 cases he found a striking association of streptococcal infections of the tonsils. Others have stressed the more or less severe concomitant dental infection.<sup>10</sup> Still others have felt that the disease is due to anaphylaxis caused by absorption of some chemical product from the intestines or other passages or from a diseased organ.<sup>11</sup>

The definite tendency of erythema multiforme to recur in the spring and fall or at certain stated intervals has been known for a long time. In other words, atmospheric influences play a role.<sup>12</sup> The precipitating effect of exposure to sunlight also has been an observation confirmed by many dermatologists. The frequent involvement of the backs of the hands and the sides and back of the neck in erythema multiforme fits in with the exposure to sunlight.

Their Relation to Syphilis, *Munchen med Wchnschr* 53 2101 (Oct 23) 1906

7 Ramel, E. Some Observations on the Causation of Erythema Exudativum Multiforme (Hebra), *Brit J Dermat* 42 1 (Jan) 1930. Percival, G. H., and Gibson, H. J. Observations on the Etiology of Erythema Exudativum Multiforme, *ibid* 43 329 (July) 1931. Hallam, R., and Edington, J. W. An Investigation of the Alleged Tuberculous Etiology of Erythema Exudativum Multiforme (Hebra), *ibid* 45 133 (April) 1933.

8 Pollitzer, S. Skin Diseases in Relation to the Sexual Organs, *New York M J* 96 669 (Oct 5) 1912. Garner, G. Erythema Multiforme Due to Hormonal Imbalance (Dermatitis Symmetrica Dysmenorrhoea), *Bull Soc franç de dermat et syph* 47 71 (Feb) 1940, abstracted, *Arch Dermat & Syph* 44 925 (Nov) 1941.

9 Guy, W. H. Erythema Multiforme, *J A M A* 71 1993 (Dec 14) 1918.

10 Semon, H. C. Dental Sepsis in Dermatology, *Practitioner* 111 199 (Sept) 1923.

11 Chalmers, A. J., and Macdonald, N. Herpes Iris, *J Trop Med & Hyg* 23 150 (June 15) 1920.

12 Zwecker, A. The Dependence of Erythema Exudativum Multiforme on Atmospheric Influences, *Arch Dermat u Syph* 163 366 1931, abstracted, *Klin Wchnschr* 11 214 (Jan 30) 1932.

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 19, 1944.

1 Forman, L., and Whitwell, G. P. B. The Association of Herpes Catarrhalis with Erythema Multiforme, *Brit J Dermat* 46 309 (July) 1934.

2 Bateman, T. *Delineations of Cutaneous Diseases*, London, Longman, Hurst, Rees & Co., 1817, plate LII.

3 Bulkley, H. D. Herpes Iris with Cases, *New York M J* 7 48, 1846.

4 Pardee, L. C. The Histopathology of Herpes Iris. Report of Two Cases, *Bull Johns Hopkins Hosp* 9 165 (July) 1898. Eichenlaub, F. J. Erythema Multiforme Complicating Vaccination, *South M J* 19 186 (March) 1926.

5 Parker, H. P., and Hazen, H. H. Erythema Multiforme Iris During the Course of Typhoid Fever, *Bull Johns Hopkins Hosp* 22 79 (March) 1911.

6 Trautmann, G. Erythema Exudativum Multiforme and Nodosum of the Mucous Membranes and

There is no doubt of the correctness of all of these etiologic observations. They, however, have led to no therapeutic successes, nor have they been of aid in the management of recurrent cases of this disorder.

#### REVIEW OF THE LITERATURE

It remained for Forman and Whitwell<sup>1</sup> to formulate a new conception as to the causation of this disease. They noted the frequent association of erythema multiforme with herpes simplex or "at least a clinical condition closely resembling herpes simplex." The associations which they noted were (1) that herpes simplex often precedes an attack of erythema multiforme and (2) that recurrent herpes simplex is common in patients with erythema multiforme.

The usual clinical sequence is as follows. The patient gives a history of repeated attacks of "cold sores" over several years, following a common cold or exposure to sunlight or wind. After the last attack of herpes simplex, at an interval of four days to two weeks, a typical attack of erythema multiforme develops. By the time the patient consults a physician there is either no trace of the previous herpes simplex or only a small crust remains. If a crust is present about the lips, it is usually mistaken for the remnant of one of the early lesions of erythema multiforme. The erythema multiforme follows its usual course and subsides. In a high percentage of cases each succeeding attack of herpes simplex is followed by an attack of erythema multiforme. In a second group of cases there are repeated attacks of erythema multiforme but without the usual preceding attacks of herpes simplex. Finally, there is a rare group of cases in which erythema multiforme has recurred over a period of years and in which herpes simplex develops for the first time after a cold or exposure to sunlight.

The many clinical similarities of herpes simplex and erythema multiforme were tabulated by Forman and Whitwell as follows: (1) their tendency to recur, (2) their occurrence mostly in spring and autumn, (3) their provocation by infections, especially the common cold, (4) their provocation by injections of serums and vaccines<sup>13</sup>, (5) their provocation in some cases by foods to which the patients are sensitive, (6) their provocation by menstruation, and (7) their provocation by sunlight.

To this group one can add the production of both entities by drugs. The production of herpes simplex by phenolphthalein is well known.

<sup>13</sup> Waugh, J. F. Erythema Multiforme, *Arch Dermat & Syph* 31:748 (May) 1935.

When erythema multiforme follows herpes simplex which has been produced by a drug, the interval between the ingestion of the drug and the development of the erythema multiforme may be so long that even when a complete history is obtained one would tend to exclude the drug as a possible etiologic factor.

Further, it may be of considerable significance that in many persons with diseases or conditions mentioned as etiologic factors in the production of erythema multiforme the occurrence of herpes simplex is common.<sup>14</sup> These include particularly pneumonia, menses and malaria.

In practically none of the cases of erythema multiforme reported before dermatologic societies or in the literature is there any mention as to the previous presence or absence of herpes simplex. There are a few exceptions to this statement. H. L. Sutton<sup>15</sup> presented a patient before the Northern New Jersey Dermatological Society on March 20, 1940. This patient presented a herpes iris of one day's duration involving the wrist. The disease had begun ten days previously with fever sores on the lips.

Patterson<sup>16</sup> related the following case history. The patient presented the unusual association of herpes iris with a herpes following the distribution of the supraorbital branch of the frontal nerve. The latter consisted of a group of eight or nine vesicles over the left eye occupying the exit point and course of the supraorbital nerve. The upper part of the chest, the shoulders, the root of the neck and the loins were the seat of herpes iris. There were no lesions on the arms and legs. Recovery was rapid, and no recurrence took place in the succeeding four months.

Even before erythema multiforme was well established as an entity, George T. Elliott<sup>17</sup> recounted a case which was undoubtedly an instance of erythema multiforme with a herpes simplex of the ear.

Walker<sup>18</sup> recorded the case of a young man who had suffered from six attacks of erythema multiforme. All of these attacks had occurred in the months of May and October. The last

<sup>14</sup> (a) Adamson, H. G. Herpes Recurrens, *Brit J Child Dis* 13:193 (July) 1916. (b) Knowles, F. C. Herpes Simplex, *New York M J* 90:256 (Aug 7) 1909.

<sup>15</sup> Sutton, H. L. Erythema Multiforme, *J M Soc New Jersey* 37:431 (Aug) 1940.

<sup>16</sup> Patterson, G. Herpes Iris, *Dublin J M Sc*, April 1890, p. 369, abstracted, *Practitioner* 45:46 (July) 1890.

<sup>17</sup> Elliott, G. T. A Contribution to the Histology and Pathology of Herpetiform Hydroa, *New York M J* 45:449 (April 23) 1887.

<sup>18</sup> Walker, W. Erythema Multiforme, *Arch Dermat & Syph* 5:137 (Jan) 1922.

outbreak had been preceded by two days by extensive herpes of the lower lip. He presented this case on account of the curious relationship between herpes labialis and erythema multiforme.

Klebe<sup>19</sup> reported on a patient with tertiary syphilis and a 4 plus Wassermann reaction who presented signs of erythema nodosum on various parts of the body. Chills and herpes febrilis led to the development of lesions of erythema exudativum multiforme on the sites of the former erythema nodosum.

These, however, are isolated instances showing a relationship between herpes simplex and erythema multiforme. By the skeptical they can be dismissed as a coincidence.

#### THERAPY

For the past ten years, repeated vaccination with smallpox vaccine has been utilized as a therapeutic procedure in the prevention of recurrent herpes simplex. It has been successful in about 80 per cent of the cases in which this procedure has been used. Even in the 20 per cent in which failures have resulted it has been of benefit in that in most of the patients the succeeding attacks of herpes simplex are milder and only a few vesicles develop. This procedure as carried out has consisted of scarifying vaccinations with smallpox vaccine. This procedure is repeated at intervals of two weeks for four or five times.

In the past few years I have utilized such repeated vaccinations for the preventive therapy of erythema multiforme associated with herpes simplex and also in treatment of erythema multiforme in which no such association could be determined. In several cases, I have felt that this procedure has been of definite value in the prevention of recurrences of erythema multiforme, especially that preceded by herpes simplex. I further believe that this procedure should be used in cases of recurrent erythema multiforme unassociated with herpes simplex.

#### REPORT OF CASES

CASE 1—O V, a woman aged 28, had her first but severe attack of erythema multiforme. This was preceded six days by a severe attack of "cold sores."

CASE 2—I H, a man aged 34, was seen during his third attack of erythema multiforme. Five lesions of herpes iris were present on the right palm and one lesion on the left palm. For the past three years he has had recurrent herpes simplex in the same area on the left side of the upper lip. He was certain that herpes

simplex of the lip had preceded the last attack of erythema multiforme but was not certain regarding such an event in association with the two previous attacks of erythema multiforme.

CASE 3—E S presented only a couple of lesions of erythema multiforme on the backs of the hands. When first seen, he also presented a subsiding herpes simplex on the left side of the upper lip. When questioned regarding the frequency of previous cold sores, he said that it had been years since he had had such a lesion.

This case is extremely interesting because of the development of erythema multiforme during ultraviolet irradiation for severe but typical pityriasis rosea. Also to be noted, without comment, is the fact that at or about the same time that the erythema multiforme developed paralysis of the right side of the face occurred. There was no sign of herpes zoster present, which excludes the Ramsay Hunt syndrome.

CASE 4—M W, a housewife aged 46, gave a history of recurrent erythema multiforme over a period of thirty years. Since 16 years of age she had suffered from two to four attacks each year. She was of the opinion that acid foods caused most of the attacks.

She was first seen on March 31, 1942 with an eruption of four days' duration. On examination she presented a moderately severe erythema multiforme of the herpes iris type involving the dorsa of the hands, the back of the neck, the eyelids and the malar regions. A few lesions were present in the mouth. On questioning, she stated that the present attack developed after a "cold sore" had appeared on her lip. This cold sore had practically disappeared when the present attack of erythema multiforme began.

She was vaccinated with smallpox vaccine at intervals of two weeks for a total of four vaccinations. During the past two years she has suffered no attacks of erythema multiforme.

CASE 5—Mrs E J, a housewife aged 36, was seen on July 20, 1942, complaining of an eruption in the mouth and about the vulva. This eruption was of four or five days' duration, first appearing about the vulva. She said that she had not had a similar eruption previously.

On examination she presented a typical erythema multiforme with a solitary lesion on the tip of the chin, on the right side of the buccal mucosa posteriorly, on the right side of the neck below the mandible and on the inner aspects of the labia minora.

Although she disclaimed a history of previous "cold sores," she presented a typical herpes simplex on the lateral aspect of the left buttock. Questioned regarding the latter eruption, she said that for years she had had similar lesions occurring in the same area or on the right buttock.

CASE 6—L W, a boy aged 17 years, was seen on Oct 19, 1939, with a severe attack of erythema multiforme involving the palms, the extensor aspects of the knees and the anterior aspects of the legs. This eruption was of two weeks' duration.

In the previous three years he had had five or six similar attacks. The first three or four had involved only the mouth. During the previous attack the first involvement of the palms had occurred. On close questioning, he recalled that the present attack and probably all previous attacks had started with a "cold sore" on the lip and later the mouth had become involved. Multiple vaccinations with smallpox vaccine were carried out. On May 5, 1944, inquiry revealed that this patient had had no more attacks since receiving two series of

<sup>19</sup> Klebe. A Case of Erythema Nodosum and Exudativum Multiforme in Late Latent Syphilis, *Arch of Dermat u Syph* 135 250 1921, abstracted, *Arch Dermat & Syph* 5 500 (April) 1922.

smallpox vaccinations the last of which was given late in 1939. He is now in the Army Air Corps.

CASE 7—Mrs E S, a housewife aged 33, was first seen Nov 8, 1940, with a second attack of erythema multiforme.

During her entire adult life she had noted a decided tendency to have "cold sores," especially after exposure to sunlight. Her first eruption of erythema multiforme was in July 1940. It began with a "cold sore" on the lip. The process then spread to involve the entire vermilion borders of both lips and finally appeared on the hands. This first attack of erythema multiforme lasted one month.

The present attack, which was the second one, began with a "cold sore," which followed exposure to sunlight three weeks previously. The cold sore rapidly developed, and one week later the eruption had appeared on the backs of the hands and forearms. Examination revealed a typical erythema multiforme of the herpes iris type involving the extensor aspects of the forearms and the dorsa and palms of the hands. There were pronounced edema, scaling and crusting of both the upper and the lower lips. Pus and blood were oozing from beneath several crusts. At this time two vaccinations with smallpox vaccine were made seventeen days apart. She was seen again Feb 20, 1942, with another recurrent attack of erythema multiforme of the iris type. This was of six days' duration. It followed the development of a large lesion of herpes simplex labialis three weeks previously. This attack of erythema multiforme was much less severe than the previous one. She now received four more vaccinations with smallpox vaccine.

On June 11, 1943 she had another recurrent attack of erythema multiforme, but this time only the lips were involved. This followed the removal of ten teeth, all except one being badly abscessed. This attack responded rather rapidly to internal administration of sulfathiazole.

Since that time she has had two or three definite but mild recurrences, all of which were associated with exposure to sunlight.

CASE 8—B B, a youth aged 20, was first seen on Aug 22, 1939, complaining of a recurrent eruption on the backs of the hands. For the past five years he had suffered from recurrent erythema multiforme to the extent of three or four such attacks each year. Each attack apparently started with a "cold sore" which practically always developed after exposure to sunlight at the beach. About the time that the "cold sore" was subsiding, the eruption on the dorsa of the hands would appear.

On examination he presented a subsiding cold sore on the left side of the upper lip. There were typical lesions of herpes iris on the dorsa of the hands and feet and the extensor aspects of the elbows and knees.

He received multiple vaccinations with smallpox vaccine. No new attacks occurred until one year later, when he was seen with a recurrence of erythema multiforme of the herpes iris type. This attack developed one week after a herpes simplex of the upper lip had appeared.

Another attack of erythema multiforme occurred in March 1941. This also followed a herpes simplex of the lower lip, starting eight or ten days after the first appearance of the herpes. At this time he was given salicylamide by mouth. He has not been seen since.

CASE 9—E B, a man aged 24, was first seen on Aug 10, 1940, with an extremely severe generalized erythema multiforme.

His history revealed that as a child he had suffered from repeated attacks of herpes labialis. During the five

years preceding his first visit he had averaged about three attacks of erythema multiforme each year. These attacks all followed the same pattern, beginning with an eruption on the lips. At times one attack was just subsiding when a new attack would occur.

On examination he presented five or six separate groups of herpes simplex involving both upper and lower lips. On the arms, legs and palms there was a generalized, discrete, pea-sized, vesicular and bullous erythema multiforme. His temperature rose to 102 F, and for a period of nearly three weeks he was ill and confined to his house. He was vaccinated four times with smallpox vaccine.

During the past three and a half years he has had only three or four attacks of herpes simplex. With one of these attacks he had two blisters on the left shin. Following another, but separate, attack of herpes simplex, he had about a dozen "blisters" scattered over the body. After this he received another series of multiple smallpox vaccinations. He has remained entirely free since this last series of vaccinations.

CASE 10—J A C, a white man aged 55, was first seen on Feb 15, 1943, with a typical erythema multiforme involving the face, the sides and back of the neck and the dorsa of the hands. This eruption was of five days' duration. During the preceding nine years he had suffered from three or four similar recurrent attacks of this disease each year.

On questioning he denied any association of cold sores with these recurrent attacks. However, he did recall that he had suffered a great deal from recurrent herpes years ago when he had worked outdoors.

In spite of the apparent absence of a history of an association with herpes simplex, therapy was begun with smallpox vaccinations. Three weeks after the last vaccination he had a mild attack of erythema multiforme. Four months later he had another mild but definite attack of erythema multiforme following exposure to sunlight. Three months later another attack occurred, and for the first time he recalled a definite attack of herpes simplex four or five days before the onset of the erythema multiforme. Although all of these attacks were milder than those which he had had before his repeated vaccinations with smallpox vaccine, it was felt advisable to give him another series of smallpox vaccinations. This was done, the fourth and last vaccination of the second series having been given on Dec 14, 1943. Since that time he has had no recurrences.

#### COMMENT

In the absence of experimental confirmation, one can only briefly speculate as to the exact relationship between herpes simplex and erythema multiforme. In the present state of knowledge it can be said that in many instances herpes simplex has some relationship to erythema multiforme. In these cases herpes simplex has a role which might be compared to that of a delayed-action bomb. Whether the eruption of erythema multiforme itself is actually produced by a virus is unknown.

Nevertheless, there are some indications that a virus may play a role in the actual production of erythema multiforme. Thus epidemics of erythema multiforme have been reported. Leip-

ner<sup>20</sup> recorded that thirty of fifty inmates in a boy's home had typical erythema multiforme. Most of the boys presented a mild coryza from eight to ten days before the outbreak of the cutaneous disorder.

Erythema multiforme has also been reported in association with lymphogranuloma venereum, a disease of proved virus nature<sup>21</sup>. In 1 instance the virus was present in the cutaneous lesions<sup>22</sup>.

Only rarely has the possibility of a virus causation of erythema multiforme been considered. One such example was the case of the patient presented by Rattner and Cornbleet<sup>23</sup> in whom a localized encephalitis with jacksonian epilepsy occurred in association with a bullous erythema multiforme. In the discussion of this case, Laymon mentioned the view of Jausion and Thevenot<sup>24</sup> that erythema multiforme is possibly a virus disease.

The occasional association of Vincent's disease<sup>25</sup> with an erythema-multiforme-like eruption must be reviewed in the light of recent work which views the virus of herpes simplex as the etiologic agent<sup>26</sup> of Vincent's disease.

The fact that in occasional cases erythema multiforme responds to drugs of the sulfonamide group<sup>27</sup> does not, in my opinion, negate the view that herpes simplex may be the initiating lesion.

Finally, in the consideration of herpes simplex as an etiologic agent of erythema multiforme, one must remember that herpes simplex is rather of frequent occurrence in areas elsewhere than

about the mouth, e. g., on the buttocks, genitalia and corneas.

## CONCLUSIONS

In a considerable percentage of cases herpes simplex is an immediate preceding lesion of recurrent erythema multiforme.

Repeated vaccinations with smallpox vaccine appear to be of value in the prevention of recurrent erythema multiforme associated with a preceding herpes simplex.

NOTE—Since this paper was prepared I have observed 2 additional cases which confirm the observations. Additional confirmation has been made by other independent observers, as noted in personal communications from Dr. Anker Jensen, of Los Angeles, and Dr. J. F. Campbell, of Fort Worth, Texas.

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## ABSTRACT OF DISCUSSION

DR. FRANCIS W. LYNCH, St. Paul. Dr. Anderson deserves credit for noting the frequent coexistence of herpes simplex and erythema multiforme. He does not claim to have established an etiologic relationship but offers a suggestion for preventive therapy for a disease regarding which most physicians feel helpless.

Negative evidence against a viral cause of erythema multiforme lies in the clinical relationship between that disease and erythema nodosum, a disease for which bacteria seem rather well established as causing the majority of cases. Erythema multiforme is frequently preceded by some minor illness, or perhaps prodromal symptoms. Possibly the herpes simplex observed by Dr. Anderson is merely a result of those early symptoms rather than a trigger mechanism which evokes the erythema multiforme.

DR. PAUL E. BECHET, Elizabeth, N. J. While Dr. Anderson's paper is a valuable contribution to the discussion of the etiologic relationship of erythema multiforme to herpes simplex, it does not in my opinion offer sufficient evidence that such a relationship exists. In an extensive clinical experience of many years I have observed the association of herpes simplex and erythema multiforme so rarely as to be convinced that the etiologic factors of the two dermatoses are entirely unrelated. The fact that herpes simplex is one of the commonest of dermatoses and that the occurrence of erythema multiforme is, in comparison, rather rare, together with the additional fact that the great majority of patients with intermittent attacks of herpes (four or more a year) for many years have never had erythema multiforme, is important evidence against Dr. Anderson's conclusions.

DR. FRED WISE, New York. The virus of herpes simplex produces definite and specific changes on the rabbit's cornea and sometimes meningitis in the rabbit.

It would seem to me that the next step, and the logical thing to do now by way of further investigation, is to inoculate the rabbit's cornea with material from vesicles of erythema multiforme and find out whether the same specific reaction is obtained, that is, keratinization of the cornea and possible meningitis.

DR. NORMAN M. EPSTEIN, San Francisco. The relation of herpes simplex to erythema multiforme is still not clear to me.

20 Leipner, S. The Epidemic Occurrence of Erythema Exudativum Multiforme, *Dermat Wchnschr* **101** 1178 (Sept 21) 1935, abstracted, *Arch Dermat & Syph* **35** 304 (Feb) 1937.

21 Goldberg, L. C., and Fonde, G. H. Recurrent "Lymphogranulomatid" (?), *Arch Dermat & Syph* **34** 478 (Sept) 1936.

22 Midana, A. The Etiopathogenesis of Erythema Multiforme in Poradenitis Inguinalis, *Gior ital di dermat e sif* **76** 1091 (Aug) 1935, abstracted, *Arch Dermat & Syph* **33** 1078 (June) 1936.

23 Rattner, H., and Cornbleet, T. Erythema Multiforme, *Arch Dermat & Syph* **40** 318 (Aug) 1939.

24 Jausion, H., and Thevenot, S. The Vicissitudes of Experimentation with Erythema Nodosum and Erythema Polymorphe, *Bull Soc franç de dermat et syph* **45** 1053 (July) 1938.

25 Crance, A. M. Vincent's Disease Associated with an Erythema Multiforme-Like Eruption, *Arch Dermat & Syph* **28** 508 (Oct) 1933.

26 Black, W. C. The Etiology of Acute Infectious Gingivostomatitis (Vincent's Stomatitis), *J Pediat* **20** 145 (Feb) 1942.

27 Bregman, A. Treatment of Erythema Multiforme Exudativum with Sulfanilamide, *Arch Dermat & Syph* **38** 623 (Oct) 1938. Combes, F. C., and Canizares, O. Sulfanilamide and Allied Compounds. Their Value and Limitations in Dermatology, *ibid* **44** 236 (Aug) 1941.



After artificial fever therapy in the treatment of syphilis, one commonly sees herpes simplex, particularly after the first episode of fever. Of several hundred patients so treated, 75 to 85 per cent have had herpes simplex, but I have not seen erythema multiforme in that group.

I have under my care a young woman who has had recurrent herpes-simplex-like lesions of her lips associated with an erythema-multiforme-like eruption of the entire mucous membrane of the mouth, without glabrous skin lesions. This woman has had these attacks for thirteen years, and has been seen by many dermatologists. She has had various diagnoses. Some physicians have said that the eruption is erythema multiforme, and others have diagnosed herpes simplex with lesions in the mouth.

She has now for the first time gone a whole year without an attack, following several series of smallpox vaccinations.

DR ANTHONY C. CIPOLLARO, New York. I should like to relate an embarrassing experience that I had three years ago when a friend of mine, a general physician, referred to me a young woman who had extensive herpes simplex of the chin (two or three such attacks each year), for whom I advised smallpox vaccination. I had read about the complications of smallpox vaccination, but I had never had personal experience with them. At the time of the patient's sixth vaccination fever, malaise and symptoms of a mild encephalitis developed. Fortunately, she recovered completely, but she was in the hospital for a considerable time.

I have been cautious about using smallpox vaccination for the treatment of herpes since that date.

DR M. H. EBERT, Chicago. It seems that the herpes virus is coming into its own. Many of you had the pleasure of listening to Dr. Lynch's excellent paper on the etiology of Kaposi's varicelliform eruption. We have a paper this afternoon by Dr. Lane on the same subject. This morning we heard that herpes virus plays some role in the causation of erythema multiforme. As Dr. Wise has said, the proof of the direct relationship should be easy. The herpes virus can be demonstrated in two ways: first, by animal inoculation, and that work was initiated by Gruter back at the time of World War I. He was an ophthalmologist. As is known, herpes simplex sometimes affects the cornea. Gruter inoculated material from a human cornea into a rabbit's eye and got "takes," got violent keratitis and in some instances encephalitis.

Lowenstein some years later took up the work and published conclusions, and that started an enormous amount of experimental work.

The interest was great because it was believed, since the herpes simplex virus is neurotropic in animals, that it was not only dermatotropic in human beings but at times neurotropic and that it sometimes would cause von Economo's encephalitis, which appeared for the first time during World War I in epidemic form.

A great deal of work has been done along this line, experimentally and immunologically, and the question of the relation of herpes virus to von Economo's encephalitis is still unsettled.

In my work, I have had occasion to do experimental work on rabbits and on guinea pigs and dogs with the herpes simplex virus using various controls. Among the controls I have used the bullae and vesicles of erythema multiforme and herpes iris and have obtained negative results. However, negative results do not mean a great deal.

Staining is another way in which the herpes virus can be demonstrated, since it is large—it measures 200 millimicrons in diameter—and it can be stained by special stains. The best stain is that introduced by Hertzberg, Victoria blue. That is not obtainable in this country at present, at least I have never been able to obtain it. Another means is use of Morosow's staining procedure, which is a silver impregnation method and is fairly satisfactory.

If the material is taken within the first twenty-four or forty-eight hours, the herpes simplex virus can be demonstrated in the vesicles. However, it is considerably more difficult to demonstrate than the virus of herpes zoster or the virus of vaccinia or the virus of chickenpox. I have been using lesions of erythema multiforme as controls for these stains. When they were negative, it was satisfying. It may be, however, that in cases of that disease and with that stain it is difficult to demonstrate herpes virus in the lesions.

I think that if the herpes virus is the direct cause of erythema multiforme the fact will shortly be experimentally demonstrated.

DR. SAMUEL AYRES JR., Los Angeles. I want to express my appreciation for the thought that herpes may be at least one of the causes of erythema multiforme.

As long as the cause of the disease is in dispute, I should like to cite 1 case in which it apparently had a definite beginning. A woman physician was scratched on her finger by a cat, and the lesion became infected, about the tenth or eleventh day after the onset, when the lesion was still infected, typical erythema multiforme, with iris-like lesions on both hands and arms, appeared. She stated that it was the first attack she had ever had. It is quite possible the herpes virus may be one of the trigger mechanisms, and in the other instances a bacterial infection may be the precipitating factor, as in this case.

DR. EDWARD F. CORSON, Philadelphia. The consideration of erythema multiforme as a virus disease appears to me possibly to justify a treatment which a group of dermatologists in Philadelphia have been using for a good many years—the intravenous injection of mercuric cyanide. This drug has served to abort the disease in many cases and is so much appreciated by patients who have recurrent attacks that they frequently come early in the outbreak for treatment of this sort. It seemed to me to be only an empiric sort of procedure.

I could not explain why we got these results, but the fact that erythema multiforme is stamped as an infectious disease seems to vindicate the use of such a treatment.

DR. NELSON PAUL ANDERSON, Los Angeles. I stressed particularly in the paper that the observations were entirely clinical. I have made no experimental inoculations.

It has been my impression, in studying the literature not only on virus diseases of the skin but on virus diseases in general, that experimental work with viruses has many pitfalls. A few years ago, when results of work on the virus of herpes simplex were published, authorities believed that this virus was the cause of epidemic encephalitis because it caused encephalitis in rabbits. Since that time I think that point of view has been changed.

I believe that one can ask every person with herpes simplex that one sees for the next ten years without finding a history of erythema multiforme, but I believe

that the process should be reversed, I suggest that patients with erythema multiforme be asked regarding the previous presence of herpes simplex.

I do not feel at all that the virus of herpes simplex causes erythema multiforme in the sense that one will ever find the virus in the lesion. I do know that this clinical observation of the frequent preexisting herpes simplex in persons with typical erythema multiforme is correct. This refers only to erythema multiforme for which there is no argument as to the diagnosis. It does not appear to be true of erythema multiforme which

one man calls a toxic bullous eruption, and another calls an atypical dermatitis herpetiformis while another man believes the disease to be pemphigus. Finally, in the management of recurrent erythema multiforme, this newer point of view offers a therapy which, while not 100 per cent successful, is at least an improvement over the present methods of treatment.

I think that this all goes to show that dermatologists are going to have to do more experimental work on virus diseases of the skin and, perhaps, utilize some of the newer methods, such as electron microscopy.

# NUTRITIONAL DERMATOSES IN THE RAT

## XI VITAMIN A DEFICIENCY SUPERIMPOSED ON VITAMIN B COMPLEX DEFICIENCY

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The lesion of vitamin A deficiency has been defined by Wolbach and Howe<sup>1</sup> as atrophy of many glands, arrest of growth, emaciation and replacement of many different single-layered epitheliums by stratified keratinizing epithelium. The process of the change from the cuboidal or columnar type of epithelium to the stratified type is known as keratinizing metaplasia, and it has been demonstrated numerous times in various epitheliums other than skin.<sup>2</sup> There is no con-

fusion regarding the primary histologic alterations and the resulting lesions of the eye, the paraocular glands and the respiratory, gastrointestinal and genitourinary systems. However, the question of the cutaneous lesion of vitamin A deficiency in the rat has been a matter of contention in many quarters, and it should be clarified. An analysis of the important early investigations of the cutaneous lesion of vitamin A deficiency in the rat explains some of the confusion, and an appraisal of more recent investigations of vitamin A deficiency in man as well as in the experimental animal brings out additional reasons why there has been so much dispute. The first published account of cutaneous alterations due to vitamin A deficiency in the rat appeared in 1918, when McCollum, Simmonds and Parsons<sup>3</sup> wrote "These groups of rats developed very rough, scaly tails and numerous bleeding points over the surface. The ears were thickened and in the margins scales developed. There was a cutaneous horn on the nose of each rat. These signs of pathological changes on the skin are common in our rat colony in animals fed certain types of faulty diet." In 1921 Steenbock, Sell and Buell<sup>4</sup> stated "A fat-soluble vitamin deficiency is also far from being conducive to normal cutaneous nutrition so that very often, especially after an age of four

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1 Wolbach, S B, and Howe, P R Tissue Changes Following Deprivation of Fat Soluble A Vitamin, J Exper Med 42:753 (Dec) 1925

2 (a) Wolbach and Howe<sup>1</sup> (b) Yudkin, A M, and Lambert, R A Pathogenesis of Ocular Lesions Produced by Deficiency of Vitamin A, J Exper Med 38:17 (July) 1923 (c) Yudkin, A M Changes in the Paraocular Glands Accompanying the Ocular Lesions Which Result from a Deficiency of Vitamin A, ibid 38:25 (July) 1923 (d) Goldblatt, H, and Bamschick, M Vitamin A Deficiency and Metaplasia, ibid 46:699 (Nov) 1927 (e) Portman, K Investigations on the Histological Changes in Skin of Rats on Various Diets, Acta path et microbiol Scandinav 4:340, 1927 (f) Tyson, M D, and Smith, A H Tissue Changes Associated with Vitamin A Deficiency in the Rat, Am J Path 5:57 (Jan) 1929 (g) Gudjonsson, S K Experiments on Vitamin A Deficiency in Rats and the Quantitative Determination in Rats of Vitamin A, Copenhagen Levin & Munksgaard, 1930, p 70 (h) Thatcher, H S, and Sure, B Avitaminosis III Pathologic Changes in Tissues of the Albino Rat During Early Stages of Vitamin A Deficiency, Arch Path 13:756 (May) 1932 (i) Chu, F T, and Murphy, A The Early Signs of Vitamin A Deficiency in Albino Rats, J Pediat 5:68 (July) 1934 (j) Mori, S Primary Changes in Eyes of Rats Which Result from Deficiency of Fat Soluble A in Diet, J A M A 79:107 (July 15) 1922 (k) Mason, K E Differences in Testes Injury and Repair After Vitamin A Deficiency, Vitamin F Deficiency and Inanition Am J Anat 52:153 (March) 1933 (l) Wolbach, S B The Pathologic Changes Resulting from Vitamin Deficiency, J A M A 108:7 (Jan 2) 1937 (m) Hou, H C



months has been reached, evidence of dermal malnutrition makes its appearance. The fur appears bushy and thin, cutaneous growths occur on the tail, ears and nose, and finally sores, which heal with difficulty, appear on the feet, limbs and body, all bear testimony to this state of malnutrition." Manville<sup>21</sup> found that there was a decreased activity of the sebaceous glands of vitamin A-deficient rats and that their "hair was bristling and dry and readily fell out." Wolbach and Howe<sup>1</sup> referred to the humped posture, rough coat, emaciation and encrusted eyelids as familiar signs of the deficiency. They made observations of the skin of the eyelids and the base of the ear where the skin was included in the preservation of the eye and in the parotid and exorbital glands, in these locations they found no striking changes. In the most advanced stages of A avitaminosis they observed slight but demonstrable atrophy of the hair follicles and sebaceous glands. The epidermis in a few instances was thinner than that in control animals, and the keratinizing layer was less pronounced. Portman<sup>20</sup> stated that the lesion of vitamin A deficiency in the skin of a rat consists of atrophy of various elements of the skin and great diminution in the number of hairs as well as in their length and thickness. However, he considered such changes not entirely specific for vitamin A deficiency. Gudjonsson<sup>28</sup> made extensive gross and microscopic observations of rats suffering with vitamin A deficiency. Regarding the skin, he observed only that the hair had lost its luster and smoothness and that there was scaling on the paws. Smith and Sprunt<sup>5</sup> found that deficiency of vitamin A as well as of vitamin B resulted in atrophy of the sebaceous glands of the tail. Munilla<sup>20</sup> stated that the first sign of vitamin A deficiency is a decrease in the length of the hairs, later the fur is bristly, and there are swollen eyelids, photophobia, pale skin, pale ears and pale tail, when the hair is shaved, there is a complete lack of regeneration in the shaved area. In a detailed description of the pathologic changes of vitamin A deficiency in rats, Hou<sup>21</sup> made only a brief mention of the skin. He stated that he had occasionally observed hyperplasia and hyperkeratinization of the epidermis. In 1936 Klotz and Holman<sup>6</sup> reviewed the subject of vitamin A deficiency and expressed the opinion that the cutaneous changes in animals

described by the various investigators were not caused specifically by deficiency of vitamin A, they suggested that the "growths on the tail, ears and nose" described by Steenbock, Sell and Buell<sup>4</sup> were due to mites. Sullivan and Evans<sup>8</sup> recently showed that complicating deficiencies of the vitamin B complex, fat and essential fatty acids in experimental diets had been responsible for the misrepresentation of the vitamin A deficiency syndrome in the past. When diets similar to those recommended in the past for the production of vitamin A deficiency were fed to young rats, the cutaneous signs which resulted were those which have been described in connection with various vitamin B complex deficiencies.<sup>9</sup> However, when young rats were fed a diet deficient only in vitamin A, there resulted a deficiency disease the gross and microscopic signs of which differed from the previously recorded descriptions of vitamin A deficiency. In uncomplicated vitamin A deficiency<sup>8</sup> there were no gross cutaneous alterations except during the very late stages of the deficiency, when it was not possible to exclude the effects of complicating deficiencies and the nonspecific effects of deficiency. Shaving experiments showed that vitamin A-deficient rats retained the ability to regrow hair until the time when body growth had ceased. In the case of rats subsisting on inadequate total amounts of food but adequate relative amounts of vitamin A and vitamin B, "hair regeneration" occurred weeks after body growth had ceased.<sup>8</sup> In various groups of rats reared on vitamin B complex-deficient diets containing adequate and inadequate amounts of vitamin A, there was a failure of regrowth of hair in the early stage of the deficiency, indicating that the sign described by Munilla,<sup>20</sup> namely, the failure of regrowth of shaved hair, was a manifestation of vitamin B complex deficiency rather than one of vitamin A deficiency. The epidermis in the early stage of uncomplicated vitamin A deficiency was of approximately normal thickness. There was dilatation of hair follicles, particularly in the upper

8 Sullivan, M., and Evans, V. J. Nutritional Dermatoses in the Rat. X Vitamin A Deficiency, *J. Nutrition* 25 319 (April) 1942.

9 (a) Sullivan, M., and Nicholls, J. Nutritional Dermatoses in the Rat. I Vitamin B<sub>6</sub> Deficiency, *J. Invest. Dermat.* 3 309 (Aug.) 1940, (b) II Skin Changes in Rats Deficient in the Entire Vitamin B Complex Other Than Thiamine, *ibid.* 3 337 (Aug.) 1940, (c) III Gangrene and Spontaneous Amputation of the Digits Produced by Combined Deficiency of Vitamin B<sub>6</sub> and the Filtrate Components, *ibid.* 4 123 (April) 1941, (d) IV Riboflavin Deficiency, *ibid.* 4 181 (June) 1941, (e) VI The Effect of Pantothenic Acid Deficiency, *Arch. Dermat. & Syph.* 45 917 (May) 1942.

half of the shaft, where the epithelial lining of the follicle was often atrophic. Frequently the sebaceous glands attached to the upper part of the sides of the shaft were dilated and their cells were completely disintegrated. The lower portion of the follicle, including the bulb, remained intact, and in many sections the hair was present and apparently structurally normal despite the dilatation and atrophy of the upper portion of the follicle, as a result of which there were dilated, thin-walled, biconcave spaces containing loosely arranged keratotic lamellae. In the late stage of the disease there were dilatation, disintegration and atrophy of the sebaceous glands in the lower portion of the follicle, with subsequent wide dilatation in the bulbar region as well as in the upper part of the follicle. In some cases the epidermis also was atrophic in the late stage. Two months after the publication of our observations Moul<sup>9a</sup> independently reported the histopathologic changes of rat skin in avitaminosis A. Although the composition of the diet in Moul's experiment differed from the composition of the diet used in our experiments, it was comparable in that it probably lacked only vitamin A. Moul's observations corresponded in many respects to those reported by us. He described dilatation and hyperkeratinization in the upper third of the shaft of the hair follicle and drew a distinction between the primary lesion for which the lack of vitamin A is specifically responsible and the secondary sequelae of general atrophy of the sebaceous glands and loss of dermal fat stores, which are not specific results of vitamin A deficiency.

In 1934 Frazier and Hu<sup>10</sup> described in Chinese soldiers a dermatosis which they termed follicular hyperkeratosis. In the majority of their patients there were ocular signs of vitamin A deficiency, and the diets of the soldiers were deficient in vitamin A. The lesion consisted of hyperkeratosis and atrophy of hair follicles followed by plugging and hypertrophy of hair follicle epithelium. After the publication of Frazier and Hu's findings and confirmatory observations of others,<sup>11</sup> all discussions of vita-

min A deficiency included summaries of the internal changes in animals and the cutaneous alterations in man. As a result of grouping the histologic alterations of skin of man and the various other epitheliums of animals, there has developed an acceptance of the concept that the cutaneous lesion due to vitamin A deficiency is similar to that of other epitheliums and that it is the result of so-called keratinizing metaplasia.

There is an important consideration that has been unappreciated in previous discussions of the subject of vitamin A deficiency of the skin. In the skin the epithelium is of the stratified keratinizing type. Therefore, keratinizing metaplasia in its literal meaning is an impossibility unless atrophy, which precedes the "metaplasia," is so profound that a single-layered epithelium is produced. Ketron<sup>12</sup> has questioned the propriety of the term "keratinizing metaplasia" as applied to the skin, even when seemingly only one or two layers of epithelial cells are present. He views the change as a shortening of the normal process of all keratinization, since the cells are of the same kind whether in normal or abnormal states, and he points out that atrophy may be associated with hyperkeratosis in various diseases of the skin in man. In Ketron's opinion it is doubtful whether the same layer of cells can fulfil the function of keratinization as well as reproduction. The following are Weidman's<sup>12a</sup> comments: "A keratinizing cell is on the way out, its normal purposeful activities can no longer be a part of the economic life of epiderm such as is connoted when metaplasias are introduced into the reactions of living tissues (whether they turn out to be useful or not). In short, 'keratinizing metaplasia' should be abandoned." Frazier and Hu<sup>10</sup> considered that keratinizing metaplasia had occurred in their patients because the follicular hyperkeratoses followed atrophy of at least a portion of the hair follicle epithelium and later there was proliferation of the epithelium near the keratinized, atrophied portion. Sullivan and Evans<sup>8</sup> observed hyperkeratinization of the upper portion

<sup>9a</sup> Moul, F. H. Histopathology of Rat Skin in Avitaminosis A, *Arch Dermat & Syph* 47:768 (June) 1943.

<sup>10</sup> Frazier, C. N., and Hu, C. K. Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man. *Arch Int Med* 48:507 (Sept) 1931.

<sup>11</sup> (a) Sweetzer, S. E. Skin Manifestation of Avitaminosis, *Minnesota Med* 16:670 (Nov) 1933. (b) Loewenthal, L. J. A. A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency, *Arch Dermat & Syph* 28:700 (Nov) 1933. (c) Nicholls, L. Phrynoderma, a Condition Due to Vitamin A Deficiency, *Indian M Gaz* 68:681 (Dec) 1933. (d) Goodwin, G. P. A Cutaneous Manifestation of

Vitamin A Deficiency, *Brit M J* 2:113 (July 21) 1934. (e) Sweet, L. K., and K'ang, N. J. Clinical and Anatomic Study of Avitaminosis A Among Chinese, *Arch Dis Childhood* 50:699 (Sept) 1935. (f) Giblin, W. E. Loewenthal's New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency Observed in Papuan Natives, *M J Australia* 1:202 (Feb 8) 1936. (g) Reiss, F. A Contribution to the Cutaneous Manifestation of Vitamin A Deficiency, *Chinese M J* 50:945 (July) 1936.

<sup>12</sup> Ketron, L. W. Personal communication to the authors.

<sup>12a</sup> Weidman, F. Personal communication to the authors.

of hair follicles in the majority of 200 rats. It was difficult to be certain whether atrophy of the epithelium always preceded the process of hyperkeratinization. However, in most of the sections the hair follicle and/or the sebaceous gland epithelium was thinned as far into the follicle as the hyperkeratinization extended, whereas the portion of the hair follicle below the "plug" was apparently normal. Proliferation of epithelium below the keratinized areas was not observed. In many cases an apparently normal hair was surrounded at the neck by thick hyperkeratosis. Macroscopic spinous processes were not observed in 200 rats. This may have been because there were no foci of hypertrophied epithelium to aid in evaginating the horny plugs. However, the amount of hyperkeratotic material may not have been sufficient to protrude out of the follicular orifice and above the surface of the skin and to produce a horny spine comparable to the Frazier-Hu lesion in man. We have shown that in experimental vitamin A deficiency, atrophy of the entire skin and its appendages occurs in the late stage, when it is impossible to exclude the effects of inanition and superimposed deficiency. We have shown also that the signs of vitamin A deficiency in the rat may be delayed by increasing the amount of vitamin B complex in the vitamin A-deficient rats and that the deficiency signs may be precipitated by inadequacy of vitamin B complex and fat in a vitamin A-deficient diet. These observations indicate an interrelationship of vitamin A and the vitamin B complex and suggest the possibility that vitamin B complex deficiency preceded or accompanied vitamin A deficiency in man when follicular hyperkeratoses were produced. If such had been the case with the soldiers of Frazier and Hu, the concept of keratinizing metaplasia might have been fulfilled. On many occasions we have discussed at length with Dr. Frazier the adequacy of the diets of the Chinese soldiers in regard to the vitamin B complex and fat content. Dr. Frazier has steadfastly maintained that so far as he could determine the soldiers' rations were inadequate only in vitamin A. However, a later report from China by Reiss<sup>13</sup> has described a similar if not identical cutaneous lesion in natives subsisting on diets known to be deficient in the vitamin B complex as well as in vitamin A.

The following experiments were planned to determine the effect of superimposing vitamin A deficiency on vitamin B complex (other than thiamine) deficiency. Thus an opportunity was provided for evaluating experimentally the effect of vitamin A deficiency on severely atrophied cutaneous epithelium. The conditions of these

experiments should have been ideal for producing keratinizing metaplasia in the skin if such a phenomenon were possible.

#### EXPERIMENTAL STUDY

*Experiment 1*—To 16 rats 21 days old was fed the following diet (diet I): vitamin-free casein,<sup>13</sup> 18 per cent, sugar, 66 per cent, melted butterfat, 8 per cent, McCollum Salts No. 51, 6 per cent, and cod liver oil,<sup>14</sup> 2 per cent. Into each kilogram of the mixture 2 mg of thiamine hydrochloride was incorporated. The experimental ration, therefore, was deficient in the vitamin B complex other than thiamine. During the ensuing four weeks the rats either failed to gain weight or lost weight. They were humped and weak. The skins were atrophic, and the furs were disheveled, in some there was diffuse alopecia. At this stage the animals were considered to have been depleted of the vitamin B complex other than thiamine; they were separated into four groups, IIA, IIB, IIC and IID, each consisting of 4 animals. The previously described diet was discontinued and replaced by the following basal diet (diet II): vitamin-free casein, 18 per cent, sugar, 56 per cent, lard, 10 per cent, and McCollum Salts No. 51, 6 per cent. Into the ration of group IIA, 10 per cent of yeast of known potency<sup>8</sup> was incorporated, and each rat in group A received a weekly supplement of 2800 units of vitamin A as percomorph liver oil. No vitamin A was added to the rations of groups IIB, IIC and IID. Viosterol in oil (Mead, Johnson and Company) supplied 460 units of vitamin D each week, and to supply vitamin E each rat received a weekly supplement of 10 mg of alpha-tocopherol (Merck). The vitamin B complex was supplied as yeast incorporated at a 10 per cent level into the diet of group IIB, at a 5 per cent level into the diet of group IIC and at a 1 per cent level into the diet of group IID. In group IIC the percentage of sugar in the basal diet was increased from 56 to 61 per cent, and in group IID the percentage of sugar in the basal diet was increased from 56 to 65 per cent because of the lower percentage of yeast.

There was an increase in weight of 20 to 40 Gm per animal one week after the vitamin B complex-deficient diet (diet I) was replaced by vitamin A-deficient diets IIB, which contained 10 per cent yeast, and IIC, which contained 5 per cent yeast, and the vitamin A control diet IIA, which contained 10 per cent yeast. The animals in the three groups immediately recovered from their almost moribund condition. They were no longer weak and humped. There was regrowth of hair, and in two weeks the animals appeared to be normal in all respects. In the control group (IIA) growth was continuous until the animals were killed at the end of the experiment. Microscopic examination of the rats in group IIA showed fully recovered normal skins. Between the eighth and eleventh weeks there was a plateau in the weight curves of the vitamin A-deficient groups (IIB and IIC), this was followed by slight and steady

13 S. M. A. Corporation

14 Mead Johnson and Company

decline in weight until the animals died (fig 1). Ocular signs of vitamin A deficiency were noted seven to eight weeks after the vitamin A deficient diets IIB and IIC were started. There were no gross cutaneous changes. Microscopic examination showed the signs previously described by us<sup>8</sup> in association with vitamin A deficiency, namely, dilatation of the upper portion of the hair follicle and plugging with hyperkeratotic material.

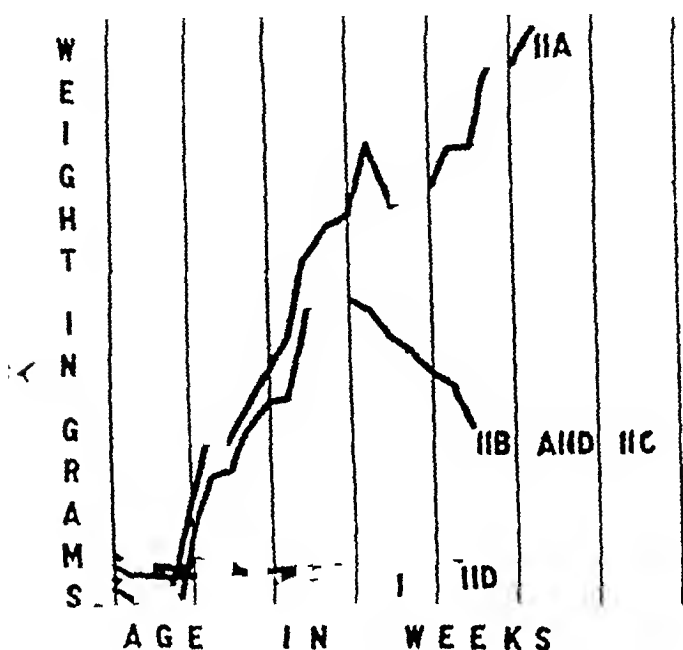


Fig 1—Curve I is the weight curve of a group of rats reared on diet devoid of the vitamin B complex other than crystalline thiamine hydrochloride. The weight at death was less than the weight at weaning. Curve II A is the weight curve of a control group of rats previously depleted of the vitamin B complex other than thiamine that were fed a diet containing adequate sources of the vitamin B complex and vitamin A. Curve II B and II C represents the gain in weight of rats previously depleted of the vitamin B complex that were fed vitamin A-deficient diets which contained 5 per cent and 10 per cent yeast as the sources of the vitamin B complex. Curve II D is the weight curve for a group of rats first depleted of the vitamin B complex other than thiamine and then maintained on a diet deficient in vitamin B (1 per cent yeast) and lacking vitamin A. At the stage when the generalized scaling was noted, this group was suffering with vitamin A deficiency superimposed on vitamin B complex deficiency. Each division on the vertical scale corresponds to 40 Gm and each division on the horizontal scale to four weeks.

There was only a slight significant difference in the weight curves of the vitamin A-deficient group IIB, which subsisted on a ration containing 10 per cent yeast, and the vitamin A-deficient group IIC, which subsisted on a ration containing 5 per cent yeast. However, in the vitamin A-deficient group IID which ingested a diet containing 1 per cent yeast as the source of the vitamin B complex after the initial period of vitamin B complex depletion (fig 1), there was

only a very slight increment of weight during the entire period of use of the vitamin A-deficient diet IID. None of the rats in this group gained more than 10 Gm, and at the end of the experimental period or at death the majority weighed less than their weights at weaning. All of the animals were weak and humped, and their appetites were poor. There was no restoration of the luster of the fur, which was uneven, short bristling and often sticky and greasy, the animals lacked interest in personal hygiene. There was a generalized scaly eruption composed of numerous discrete squamous plaques which were more abundant on the back. Microscopic examination showed thick, loose hyperkeratosis and atrophy of the epidermis, sebaceous glands and cutis (fig 3). In some sections the hyperkeratotic lamellae filled in widely dilated follicular spaces or indentations in the wavy atrophic epidermis. These collections of corneous material were responsible for the production of the squamous plaques that had been observed grossly.

*Experiment 2*—To a group of 21 day old rats, totaling 32 animals, was fed a modification of diet I. Percormorph liver oil was used as the source of vitamin A, and lard was substituted for butter as the source of fat, otherwise the diet was similar to diet I.

The purposes of this experiment were (1) to reproduce in a larger number of animals the gross and microscopic cutaneous signs which were observed in group IID, (2) to compare the effects of a basal diet containing lard with those of a basal diet containing butter and (3) to compare the effect of a single large supplement of vitamin A administered at the beginning of the experiment with those of the same dose distributed fractionally during the first period of the experiment, when the rats were being depleted of the entire vitamin B complex other than thiamine. The results of the experiment were similar to those in group IID except that the scaling and hyperkeratotic plaques appeared two or three weeks later. This was due probably to a slower initial depletion period. No significant differences were observed in the groups given supplements of single and of divided doses of vitamin A in the initial depletion period.

The appreciation of the specific effects of a deficiency must await the perfection of an experimental diet deficient in only one factor. Until recently the diets employed for the production of vitamin A deficiency in the rat were deficient in the vitamin B complex, fat, essential fatty acids, and occasionally in vitamin E. Inasmuch as there were complicating deficiencies in all of the important investigations of vitamin A deficiency, it is no wonder that the cutaneous lesion was misrepresented. An unusual set of circumstances was brought about by Frazier and Hu's<sup>10</sup> discovery of a cutaneous lesion in man which they considered to be the result of vitamin A deficiency. Thereafter the erratic cutaneous changes observed in vitamin A-deficient rats

were overlooked, and reviews dealing with the subject grouped the changes observed in human skin with the changes in various other epitheliomas of experimental animals. This was an

make valid a general scheme for one species, it was our original aim to perfect a vitamin A-deficient diet and thereby produce a cutaneous lesion which was specifically the result of a



Fig 2—4, back of a rat that was depleted first of the vitamin B complex other than thiamine and later maintained on a diet deficient in vitamin A as well as in vitamin B complex. The character of the eruption is that of a diffuse, loose, generalized scaling. B, the early stage, before scaling is generalized. There are small discrete squamous plaques which should not be confused with the discrete follicular spinous processes described by Frazier and Hu<sup>10</sup> and others.<sup>11</sup>

example of substituting the findings in one organ, the skin, of one species, man, in the scheme of findings in various organs other than skin for another species, namely, the rat. In order to

deficiency of vitamin A in the rat. To our surprise there were no gross cutaneous signs of vitamin A deficiency in uncomplicated vitamin A deficiency of the rat.<sup>8</sup> However, there were

one species,  
a vitamin A  
a cutaneous  
result of

found certain microscopic alterations<sup>15</sup> suggestive of the changes described by Frazier and Hu.<sup>16</sup> Furthermore when we compared signs of uncomplicated vitamin A deficiency with signs produced by vitamin A deficiency complicated by vitamin B complex deficiencies, we found that not only had we demonstrated the reason

complex in the vitamin A-deficient diet, and the signs of vitamin A deficiency were accelerated and intensified by vitamin B complex deficiencies and deficiencies of fat in the vitamin A-deficient diets. Popper, Steigmann and Dyniewicz<sup>17</sup> showed that when hepatic damage was produced experimentally in rats the damaged

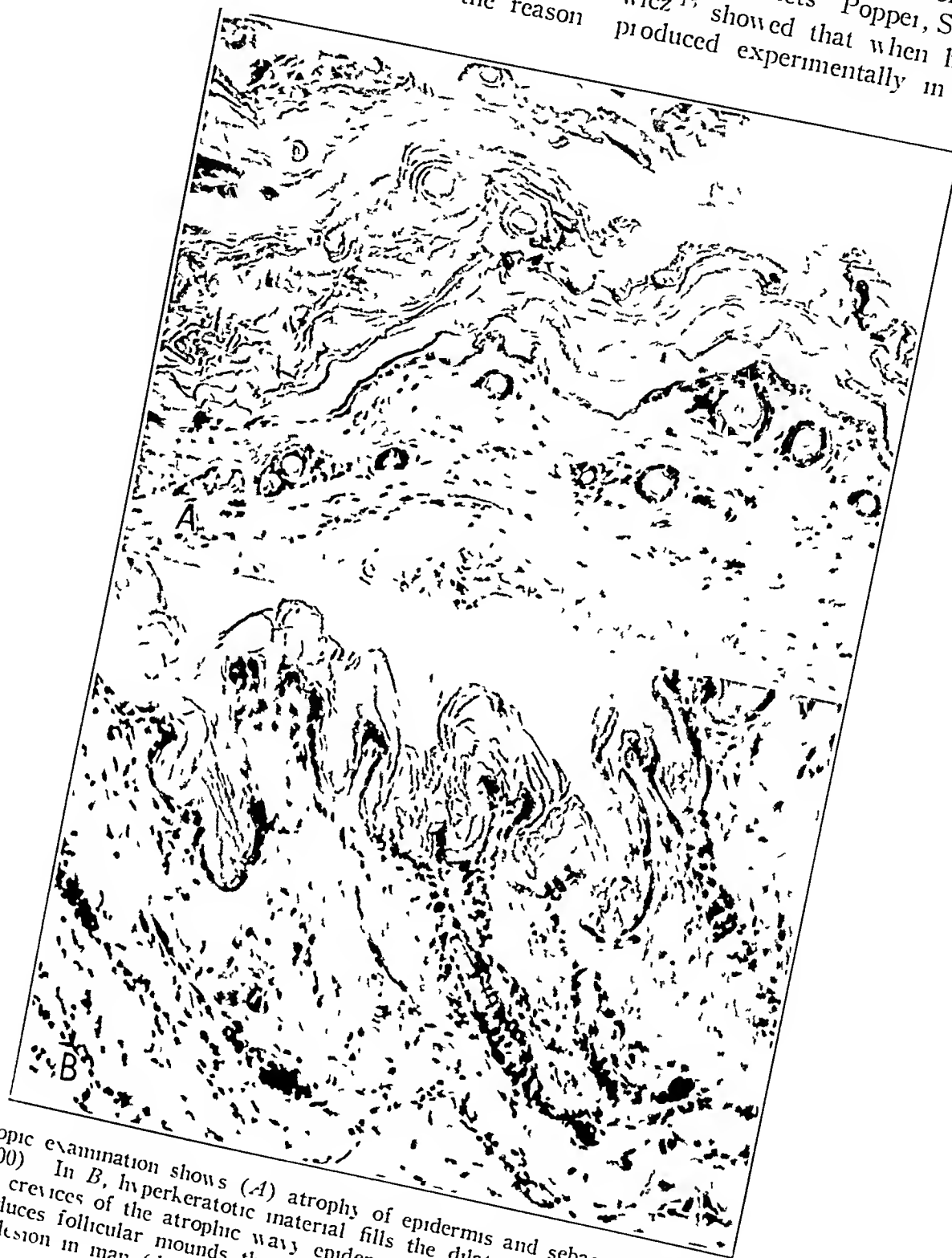


Fig 3—Microscopic examination shows (A) atrophy of epidermis and sebaceous glands and loose hyperkeratosis (dorsum  $\times 200$ ). In B, hyperkeratotic material fills the dilated upper portions of some of the atrophic hair follicles and the crevices of the atrophic wavy epidermis. Note that there are no areas of hypertrophied epidermis which produces follicular mounds through which spicules may protrude to produce a gross lesion similar to vitamin A lesion in man (dorsum  $\times 200$ ).

of the misrepresentation of the cutaneous signs of vitamin B complex deficiency but that there was signs of vitamin A deficiency in the rat. It was an interrelationship of the signs of vitamin A deficiency by increasing the amount of the vitamin B

areas in the liver contained more vitamin A than the uninvolved areas of the liver and the injured areas more slowly released vitamin A than it

<sup>15</sup> Popper H, Steigmann, F, and Dyniewicz H A Distribution of Vitamin A in Experimental Liver Damage Proc Soc Exper Biol & Med 50:266 (June) 1942



was released by the normal areas of the liver. It is not unlikely that there is less hepatic damage in rats reared on diets deficient only in vitamin A than in rats subsisting on vitamin A-deficient diets complicated by other deficiencies which are capable of producing various types of disease of the liver. The explanation for the interrelationship of the vitamin B complex, fat and vitamin A deficiency may have its basis in these facts

ciency. In the original depletion period a diet devoid of the vitamin B complex other than thiamine was fed until the skin and appendages of the rat were atrophic and the rat was practically moribund. Vitamin A was then withdrawn and the vitamin B complex was added in an amount barely sufficient to maintain life. Thus vitamin A deficiency was produced in sick rats with atrophic single-layered cutaneous epithelium and

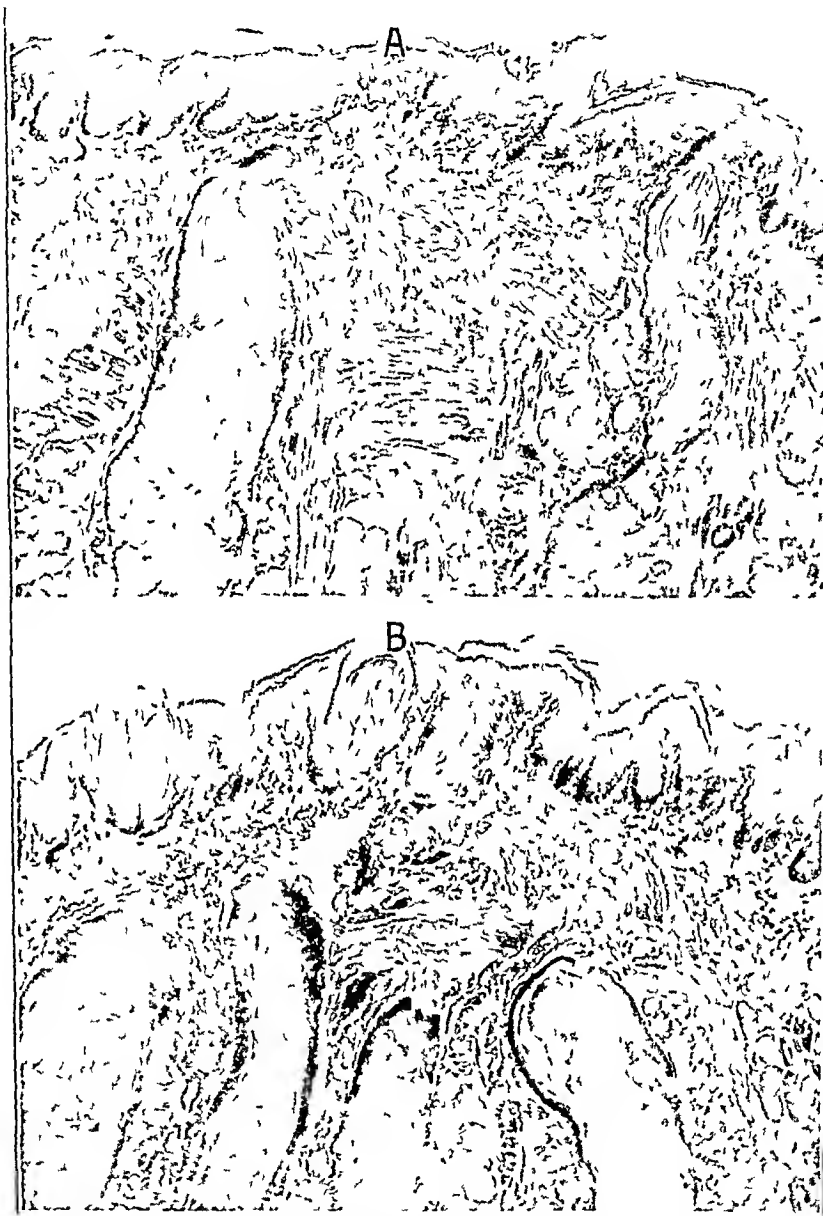


FIG. 4—Sections from base of tongue ( $\times 60$ ) of vitamin A-deficient rats. This is an illustration of the change known as keratinizing metaplasia. Note the proliferative changes in the gland ducts at the base of the tongue.

Having produced a microscopic cutaneous lesion of vitamin A and having demonstrated an interrelationship of the vitamin B complex and vitamin A, the next step was to determine whether a cutaneous lesion grossly similar to the Pizzic and Hu lesion could be produced in the rat. Experiments 1 and 2 were planned in order to demonstrate the effect of superimposed vitamin A deficiency on vitamin B complex defi-

ciency. These circumstances provided the nearest approach for producing, or, more precisely, for reproducing, "keratinizing metaplasia" from a single layer of epithelium, and at the same time there was an opportunity for observing the effects of the combined deficiencies. The resulting microscopic cutaneous alteration consisted of only a partial restitution

of the epithelium and the production of excessive keratinization in the widely dilated and atrophied follicles and in the wavy epidermis. There was no hypertrophy of portions of the hair follicle epithelium such as Frazier and Hu reported in Chinese soldiers. The collections of excessive hyperkeratinization accumulated to form small squamous plaques rather than horny spicules. There were no mounds of epidermis with craters from which the horns projected, and this was probably due to lack of proliferation of hair follicle epithelium. On casual glance there may be some resemblance of the lesion of the rat to the conventional notion of the gross lesion in the human adult, but a critical appraisal of the gross changes viewed in conjunction with the microscopic changes will demonstrate the dissimilar features of this and the original Frazier and Hu lesion. In differential diagnosis the cutaneous disease of rats most likely to be confused with this disease is fat deficiency. Frazier, Hu and Chu<sup>16</sup> recently showed that in infants

and prepubertal children suffering with vitamin A deficiency follicular damage is rare and hypertrophy of epidermal cells, usually seen in adults in similar circumstances, is not present. They presented evidence that there is a progressive development of follicular hyperkeratosis which is correlated with the subjects' age. In our experiments recently weaned rats were studied. At some future date the experiments will be repeated to determine whether there is a correlation of the development of follicular hyperkeratosis with the age of the rat.

#### SUMMARY

Young rats were depleted of the vitamin B complex other than thiamine hydrochloride. When the skin was atrophied and consisted of a single layer of epithelium, vitamin A was withdrawn from the diet and the vitamin B complex was supplied in an amount barely sufficient to maintain life. There resulted a generalized cutaneous lesion consisting of numerous small scattered squamous plaques. Microscopic examination showed atrophy of the epidermis and appendages, dilatation of atrophic hair follicles and excessive hyperkeratinization.

<sup>16</sup> Frazier, C. N., Hu, C., and Chu, F. Variations in Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty, *Arch. Dermat. & Syph.* **48**: 1 (July) 1943.



# TREATMENT OF LUPUS ERYTHEMATOSUS DISSEMINATUS BY INTERNAL ADMINISTRATION OF IODINE

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Some time ago my attention was directed, purely by accident, to the possible value of iodine given internally in the treatment of disseminated lupus erythematosus

I was called in consultation to see a patient suffering with this disease, the diagnosis having been made by Libman and Sacks and confirmed by two dermatologists. I suggested, among other things, that a thorough laboratory investigation be made for possible foci of infection. About two weeks later I was amazed to see this patient enter my office, seemingly perfectly well and without a vestige of his former generalized eruption. He had come in to ask my advice about his going to Atlantic City for a rest. The patient stated that since I had seen him he had been given some sort of dye in preparation for roentgenograms of the gallbladder and a gastrointestinal series. The dye had made him deathly ill, producing severe chills followed by a high fever (the temperature reaching 105 F), nausea and profuse and almost continuous diarrhea that lasted thirty hours. However, as his reactions subsided, all the symptoms of lupus erythematosus disappeared.

The radiologist who had taken the roentgenograms told me that the dye contained iodine and phenolphthalein and that the patient had had no other medication while he was in the hospital. I wondered at first whether it could have been the extreme dehydration and the high fever that had caused his symptoms to disappear. Then, recalling the beneficial results I had frequently observed in fixed types of discoid lupus erythematosus when the lesions had been painted with strong solution of iodine, I decided that in all probability it was the iodine which had been the healing agent. I then resolved to give it internally at the first opportunity. Subsequently I treated 5 patients with disseminated lupus erythematosus by this method. It is my purpose in this paper to report the apparently successful results of the administration of iodine by mouth

to 5 patients with disseminated lupus erythematosus

This disease is generally regarded as serious, and, while in a number of cases there have been remissions or exacerbations or both under treatment with any one of a variety of remedies or even occasionally without treatment at all, most dermatologists are agreed that the outcome is usually fatal. Banks<sup>1</sup> stated that the mortality of acute types exceeds 90 per cent and that of the mild types averages 50 per cent. Cornbleet<sup>2</sup> reported on 3 patients with acute and subacute forms of disseminated lupus erythematosus who were favorably influenced by injections of liver extract. Two of his patients subsequently died. Hopkins<sup>3</sup> cited an instance of acute disseminated lupus erythematosus apparently precipitated by roentgen rays and also apparently cured by sulfanilamide.

Every physician knows that it is sometimes difficult to recognize the various types of lupus erythematosus, particularly when few or no constitutional symptoms are present. As has frequently been pointed out before, the symptoms of this disease are easily confused with those of dermatomyositis, scleroderma and acute rheumatic fever. The pathologic changes are also, strikingly similar to those that occur in the three diseases just mentioned, all affecting principally the vascular system.

Klemperer, Pollack and Baehr<sup>4</sup> expressed the opinion that lupus erythematosus is a disease of connective tissue causing widespread alteration of the collagen fibers. They stated further that

1 Banks, B. M. Is There a Common Denominator in Scleroderma, Dermatomyositis, Disseminated Lupus Erythematosus, the Libman-Sacks Syndrome and Polyarteritis Nodosa? *New England J. Med.* **225**: 440 (Sept. 18) 1941.

2 Cornbleet, T. Acute and Subacute Disseminated Lupus Erythematosus. Treatment with Liver Extract, *Arch. Dermat. & Syph.* **43**: 829 (May) 1941.

3 Hopkins, H. H. Acute Disseminated Lupus Erythematosus. Precipitation by Roentgen Rays and Cure with Sulfanilamide, *Arch. Dermat. & Syph.* **43**: 833 (May) 1941.

4 Klemperer, P., Pollack, A. D., and Baehr, G. Diffuse Collagen Disease. Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma, *J. A. M. A.* **119**: 331 (May 24) 1942.

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the straightening and thickening of the collagen fibers, their apparent friability, their intense eosinophilia and refractibility, together with visible increase in the ground substance can be due only to a profound physicochemical aberration of the colloid state of the connective tissues."

There are many views as to the cause of lupus erythematosus, the two most widely accepted being tuberculosis and streptococcic infection. Jager<sup>5</sup> cited 2 cases of acute lupus erythematosus, in each of which there were clinical and laboratory findings suggestive of adrenal insufficiency. In neither case, however, was the complete syndrome of Addison's disease present.

I have always felt that the behavior of acute and subacute lupus erythematosus, as well as the pathologic changes, are suggestive of infection. Postmortem examination of 1 of my office patients a number of years ago showed all the serous cavities filled with fluid, endocarditis with vegetations on the cardiac valves and congestion of the liver, spleen and bone marrow, all of which are strikingly similar to conditions observed in streptococcic infection, but all smears and cultures were negative for pathogenic organisms, as were the many cultures of blood taken during the patient's illness.

Whatever the cause of lupus erythematosus disseminatus, one point stands out clearly in the cases of patients I have observed. Each one gave a history that exposure to light or severe sunburn always preceded the appearance of the cutaneous lesions.

#### REPORT OF CASES

##### CASE 1—*Subacute disseminated lupus erythematosus*

Mrs. S. B., a 27 year old white woman, was admitted to City Hospital in January 1944, for treatment of a generalized erythematous, scaly eruption with constitutional symptoms of five months' duration.

**Past History**—The patient's past, personal and family histories were irrelevant. She had always been well until 1941, when she had a severe streptococcic sore throat. For two years thereafter she suffered from migratory articular pains affecting the toes, ankles, knees, fingers and wrists and characterized by the recurrence of small red tender spots over the affected joints, often accompanied by a general swelling and stiffness of all the joints.

**Present Illness**—The present illness began five months prior to admission with a red, itching, scaling sunburn-like eruption on the face and upper part of the chest following prolonged exposure to the sun. Most of the hair in front, on the temples and on the back of the scalp fell out. She had a fever and lost weight. The temperature would often be normal for several days or weeks and then rise as high as 104 F without any apparent cause. She was studied thoroughly in another hospital, where results of all tests were found to be

essentially normal, including the blood count. About three months ago an abscess which had developed on the right heel was opened and much pus drained. Cultures of this pus showed many hemolytic streptococci. She had lost 35 pounds (15.9 Kg) in weight in a period of five months, was weak and complained of dull pains in her joints.

**Examination**—Examination showed a thin, apparently seriously ill young woman in bed with a generalized eruption covering the entire face, neck, upper part of the chest and extensor surfaces of the extremities, with blotchy, erythematous, scaly patches over most of the other parts of the cutaneous surface. The lesions, which were dry, were most pronounced on the sides of the face, bridge of the nose, scapular regions and outer surfaces of the arms. There were some telangiectasia and adherent dry scales. Her finger tips were dark blue and scaly, with dilated blood vessels. In places there was apparent atrophy, most evident over the scapulas and around the elbows.

Results of the general physical examination were otherwise normal except for a low-pitched, soft, systolic murmur over the precordium, heard best at the apex. The lungs were clear, the abdomen soft and flabby and the liver and spleen not palpable. All the deep reflexes of the upper and lower extremities were normal. The pupils were equal and reacted readily both to light and in accommodation. Examination of the fundi revealed a toxic retinitis in both eyes, a slight elevation of the disks and exudates. Her weight was 76 pounds (34.5 Kg). Her temperature was 103 F, her pulse rate 110 and her respiratory rate 22.

**Laboratory Data**—The results of the examination of the blood were as follows: hemoglobin content, 84 per cent, red blood cells, 3,700,000 per cubic millimeter, and white blood cells, 5,200, with a normal differential count. The sedimentation rate was not increased. The blood chemistry was within normal limits. Repeated cultures of the blood were negative for pathogens. The urine showed a trace of albumin but no porphyrin. Neither the electrocardiogram nor the roentgenogram of the chest revealed any abnormality. On examination the bone marrow was normal.

**Treatment**—Treatment consisted of three blood transfusions (250 cc each) given at five day intervals, a high caloric diet (3,600 calories per day), vitamins and 3 drops of 7 per cent tincture of iodine three times a day. Boric acid ointment was applied locally. The patient's progress was rapid. She gained in weight, the pains in her joints became less severe, her temperature fell to normal, and the rash showed a change for the better. After she had taken the iodine for three weeks, the eruption disappeared almost entirely, except for patches of erythema and scaling, mainly over the scapulas, elbows, knees and fingers. At this time a large fluctuating abscess the size of a lemon developed on the right side of the upper jaw and a similar one on the outer aspect of the right thigh. There was no local pain, tenderness or redness of the skin covering these swellings. The administration of iodine was stopped. The abscesses were punctured, and a thin, gray, puslike material exuded. A culture of this pus yielded *Staphylococcus aureus*. The wounds healed rapidly, and twelve days later the use of iodine was resumed. During her stay in the hospital the patient contracted erysipelas of the right side of the face, for which she was given sulfathiazole. She reacted badly to the drug, having a sulfathiazole dermatitis and symptoms of depression, lost weight and felt ill. She gave a history of having been given sulfanilamide on two previous occasions, with a similar reaction each

<sup>5</sup> Jager, B. V. Disseminated Lupus Erythematosus. Report of Two Cases with Unusual Clinical Manifestations, *Arch. Dermat. & Syph.* 46:362 (Sept) 1942.

time Use of the drug was discontinued, and she recovered promptly She continued to gain in strength and weight, the articular pains lessened, and when after four months of treatment, she was given a leave of absence from the hospital for three weeks she was entirely free from all cutaneous lesions and had gained a total of 8 pounds (3.6 Kg) in weight On her return she was better in every way and still free from all lesions

At the time of writing the patient is 15 pounds (6.8 Kg) heavier and seems remarkably well, and her only complaint is of transient pains in the joints of the fingers and in the wrists, occurring usually in the evening The skin shows only light-colored leuko-dermic areas and brown macular areas The hair has grown back on the areas of the scalp where it had come out before She is continuing the iodine treatments

*CASE 2—Lupus erythematosus disseminatus and lichen-planus-like eruption due to gold*

R S, a 61 year old white man, consulted me in January 1943, complaining of a generalized eruption of ten months' duration

*Past History*—His past and family histories were essentially irrelevant

*Present Illness*—The present illness began with pea-sized to dime-sized dark red spots on the shins, accompanied by soreness in the muscles of the legs His physician made a diagnosis of rheumatism and prescribed tablets The eruption cleared in one week Three weeks later red scaly areas appeared on top of his scalp and one on the right side of the nose, with a redness and swelling of the ears which the patient described as looking like "red cabbage" A diagnosis of lupus erythematosus was finally made, and the patient was given intravenous injections of sodium gold thiosulfate and intramuscular injections of a bismuth preparation After five injections of gold and five of bismuth the rash spread over the entire face and neck and the patient became so sensitive to light that the treatment was discontinued Daylight or lamp light caused the skin to itch and burn severely and to smart all over with "needles and pins" sensations He was then given solution of potassium arsenite By this time the rash had covered most of the body and the extremities including the soles and palms The patient was seriously ill for three weeks, and his recovery was impaired of His temperature ranged from 102 to 103 F He became weak and lost weight Lichenoid bluish red papules which were thought to be lichen planus formed at the borders of the red scaly lesions on the backs of the hands and on parts of the trunk Histologic examination confirmed the clinical suspicion Sores developed on the mucous membranes of the mouth and along the borders of the lips The feet and hands became blue, swollen and painful and tender to touch

*Examination*—Physical examination revealed a fairly well nourished and well developed white man who was obviously uncomfortable but did not appear seriously ill The heart abdomen liver and spleen were essentially normal The deep reflexes of the upper and lower extremities were normal The pupils were equal and reacted well both to light and in accommodation The skin of the face ears and back of the ears and more especially, of the neck and upper portion of the chest was light to dark red with thickening and scaling There were red shiny pea-sized to dime-sized papules at the margins The entire vermilion border of the lower lip was red and scaly On the trunk, reaching to the waist line but more especially on the upper part and over the upper extremities, the skin was mottled and dark brown with some areas of apparent atrophy

and telangiectasia the size of a pea or dime The palms and soles and the toes and fingers were bluish red, shiny and soft, and both feet and hands were deeply cyanotic There was superficial scarring along the palmar surfaces of most of the fingers of both hands A biopsy specimen from one of the papules showed lichen planus A later specimen from the scalp plaque showed possible lupus erythematosus

*Laboratory Data*—Examination of the blood showed a hemoglobin content of 76 per cent, 3,900,000 red blood cells, and 7,800 white blood cells, per cubic millimeter, of which 68 per cent were polymorphonuclear neutrophils, 4 per cent polymorphonuclear eosinophils, 16 per cent lymphocytes and 12 per cent monocytes The urine showed only a trace of albumin The Wassermann reaction was negative The blood chemistry was normal

*Treatment*—The patient was given a high caloric diet, injections of sodium thiosulfate, crude liver extract intramuscularly, magma of bismuth N F locally and strong solution of iodine U S P (3 drops increasing to 9 drops three times a day) He has taken this at intervals for about a year His condition has gradually and continuously improved, and his eruption has disappeared He is no longer sensitive to light and is able to work in his garden without difficulty He says that his feet are better in warm weather but that on hot days the feet and hands sweat profusely and swell Extreme cold produces cyanosis and tingling in the feet and hands He recently took nicotinic acid for three days, against the advice of a dermatologist, but had to stop because of flushing and tingling of his hands and feet

*CASE 3—Disseminated lupus erythematosus*

W H, a 51 year old white man, was admitted to the hospital on June 7, 1943, with a generalized eruption of nine weeks' duration

*Past History*—His past history was essentially unimportant except for curvature of the spine which had been present since early childhood He had had shortness of breath and a sensation of pressure over the heart on exercising for ten years, symptoms attributed by his physician to excessive indulgence in alcohol and excessive smoking He also had frequent pains in the right scapular region He had always been constipated Ten years ago a diagnosis of peptic ulcer had been made He was treated for this disease and was supposedly cured All of his teeth except two had been extracted because of the ulcer

*Family History*—The patient's mother died at the age of 62 from uremia and his father at the age of 61 from cerebral hemorrhage One brother died of tuberculosis one and one-half years before I saw the patient, and another died from a ruptured blood vessel of the heart Five other brothers and sisters were living and well

*Present Illness*—The present illness began two and one-half months before admission, following sunburn manifesting itself as a bright redness of the nose cheeks bald scalp, entire face, neck and upper part of the chest Instead of the sunburn's clearing, a red, blotchy eruption remained in the affected parts and gradually spread to the periphery to involve the greater part of the trunk the upper and lower extremities and, more particularly the extensor surfaces of the upper extremities and from the knees down The parts became a dark, almost purple, red and scaly The patient was not particularly ill but tired easily on exertion and felt restless and uneasy and at times weak His local physician diagnosed the eruption as sunburn A dermatologist whom he saw later considered it to be lupus erythematosus and

treated him with local applications of a soothing nature and with injections of calcium gluconate. But the eruption still continued to spread.

**Examination**—Physical examination showed a well developed and well nourished man, who, with the exception of a spinal curvature, had no physical abnormalities whatsoever. His blood pressure was 120 systolic and 74 diastolic in both arms. There was an occasional extrasystole over the heart.

The scalp, ears, face and neck and the upper part of the chest and back were covered with a uniform, dark to light, finely desquamating, red, macular and blotchy eruption, and a few areas from pinhead size to the size of a fifty-cent piece were scattered over the remaining parts of the trunk. The legs from the knees down, as well as the dorsum of the feet and toes, were dark red, with scattered petechial hemorrhages. Some areas were slightly scaly. There was no atrophy or telangiectasia. The mucous membranes were clear.

**Laboratory Data**—The hemoglobin content, red and white blood cell counts and platelet count were all essentially normal. The serum cholesterol level was 239 mg per hundred cubic centimeters, the blood sugar level 93 mg and the serum nonprotein nitrogen level 27 mg. The urine was normal. A tuberculin test elicited negative reactions with dilutions of both 1:1,000,000 and 1:100,000. The Wassermann and cephalin flocculation reactions were both negative.

An electrocardiogram revealed no abnormalities except for one premature beat. Roentgenograms of the heart, jaw, gallbladder and chest showed them to be normal. A roentgenogram of the sinuses showed evidence suggestive of some chronic pathologic changes in the right frontal and right ethmoid sinuses. Roentgenograms of the cervical portion of the spine showed a hypertrophic spur projecting downward from the lower anterior surface of the sixth cervical vertebra. There was a low irregularity in density of the lower anterior portion of this vertebral body. Otherwise the vertebral bodies, the intervertebral disk spaces and the lateral articulations appeared normal. Roentgenograms of the dorsal portion of the spine showed decided kyphoscoliosis, with the apex of the curve directed to the right. There was a generalized decalcification of the bones of the spine. The vertebral bodies from the fifth to the ninth dorsal vertebra showed anterior wedging, the degree of wedging becoming increasingly more severe toward the apex of the curve at the seventh. Bodies of the vertebrae of the thoracic portion of the spine from the fifth to the ninth thoracic vertebra were not remarkable. There was also some narrowing of the left side of the bodies of those vertebrae in that portion of the spine which showed the greatest curvature—that is, from the fifth to the ninth vertebra. The disk spaces on the left side were slightly narrowed also in this area, but otherwise they showed no remarkable change.

The patient was discharged from the hospital at the end of one week after the completion of this investigation and was readmitted on August 2 for treatment. During the first week of his stay in the hospital his temperature varied from 98.5 to 99 F. Treatment was with iodine, first painted on the localized areas and later administered by mouth. Three and five-tenths per cent tincture of iodine was applied to the face, forehead, chest, upper part of the back and shoulders. Later its strength was increased to 16 per cent, but its use had to be stopped almost immediately on account of a dermatitis which developed soon after it was first applied. Strong solution of iodine U. S. P. was then given by mouth 3 drops three times a day at first and

gradually increased to 10 drops three times a day. All of the cutaneous lesions gradually improved, and the patient felt better in every way. He gained in weight and was discharged on August 24, much improved.

He has been free of all lesions since December 1943. There is now only depigmentation and hyperpigmentation over most of the parts formerly affected. He has continued treatment at his home, coming to the office once a week. Treatment has consisted of iodine applied locally for a few days, alternated with strong solution of iodine U. S. P. or tincture of iodine by mouth, in addition to vitamins by mouth and a high caloric diet. His general health has greatly improved, he has gained about 15 pounds (6.8 Kg) in weight, and he is feeling in perfect condition.

#### CASE 4—*Subacute discoid lupus erythematosus superimposed on disseminated lupus erythematosus*

Mrs. I. H., a 42 year old white American housewife, was admitted to the hospital on Sept. 20, 1941, complaining of redness and scaling of the skin on the face, upper part of the chest, upper extremities and legs of two months' duration.

**Family History**—Her mother died in 1937 of carcinoma of the uterus. Her father died at 52 of heart trouble. She has two healthy children aged 10 and 19. The family history is otherwise irrelevant.

**Past History**—The patient had measles, diphtheria, scarlet fever and whooping cough as a child. She had two severe sunburns, one at the age of 15 and another three years before admission. One year later she consulted a physician about a bald spot on the front of the scalp. She said the biopsy from the area showed lupus erythematosus. She had no other lesions at the time. She was treated with injections of a bismuth preparation. In February 1939, a week or two after the extraction of two devitalized teeth, an eruption, which was smooth and red but not rough, appeared all over the face and chin. She was given three more injections of bismuth, after which the redness disappeared. She had no further trouble until her present illness.

**Present Illness**—In July 1941 after two weeks' exposure to the sun at the seashore, the patient's neck, face, upper part of the chest and upper and lower extremities, parts not covered by her bathing suit, became red, although, unlike sunburn, there was little soreness. Two weeks later the shins became dark red. The only subjective symptom was a slight itching. She consulted a physician, who again gave her injections of the bismuth preparation, this time without any improvement. The parts became dry and slightly scaly.

**Examination**—Examination showed a well developed and well nourished woman, apparently not seriously ill. The general physical examination was essentially non-contributory. On both sides of the face and cheeks and on the chin and the front and sides of the neck, the upper portions of the back and chest, the upper extremities and the legs from the knees down was a blotchy, macular, light to dark erythematous eruption with scaling in some areas, and the legs showed some small petechial hemorrhages. There was no telangiectasia or atrophy, nor were there any pustulous follicles. On the front of the scalp, just back of the hair line on the forehead, was a white bald atrophic area 5 cm in diameter.

**Laboratory Data**—The hemoglobin content, red and white blood cell counts and platelet counts were all normal. The serum nonprotein nitrogen level was 23 mg per hundred cubic centimeters. The Wassermann and cephalin flocculation reactions were both negative. The tuberculin test elicited negative reactions with

dilutions of 1 1,000,000 and 1 100,000. A culture from the throat showed no hemolytic organisms. An electrocardiogram and roentgenogram of the heart were both normal. Roentgenograms of the sinuses and of the gallbladder showed no abnormalities. Roentgenograms of the chest revealed calcifications in the left hilar and left pulmonary fields, as well as in the left cervical region. A biopsy of the skin showed some hyperkeratosis and a fairly narrow but easily discernible granular layer with atrophy of parts of the epidermis. Some of the superficial capillaries were dilated. Small foci of lymphocytic infiltration were found perivascularly situated. There were similar changes about the hair follicles. A definite edema was also noted. The changes were consistent with a diagnosis of lupus erythematosus, although they were not those of a well developed case.

The patient was given 3 drops of strong solution of iodine U S P three times a day, and the right upper extremity was painted with 3 per cent tincture of iodine. Her improvement was rapid. The entire skin was almost clear when she was discharged, five weeks after admission. The arm that had been painted with 3 per cent tincture of iodine was the last part of the skin to become normal, the nonpainted portions having recovered some weeks earlier. The patient has been well for more than two years.

#### CASE 5—*Lupus erythematosus disseminatus*

Mr I L., a 47 year old, single, Swedish-American engineer on a tanker, was first seen on April 5, 1943, complaining of a widespread red scaly eruption following exposure to the tropical sun five months previously.

**Past History**—He had never been ill except for typhoid in 1912. While he was in the tropics in 1934 he sustained a bad sunburn, which left red areas over most of the exposed parts. Since then any exposure to strong sunlight has caused an acute flare-up of the eruption. He has always been well in cool climates and when his skin was protected from the sun.

**Present Illness**—The present attack began while the patient was in the tropics in December 1942, starting with a redness and burning of the parts of the body not covered by a bathing suit, so severe that it "almost drove him out of his mind." He saw several physicians, one of whom suggested the diagnosis of lupus erythematosus. Various local remedies were applied, without any benefit. He has never had any constitutional symptoms, except for a feeling of fatigue and some irritability from the local discomfort.

**Examination**—Physical examination revealed a well developed and well nourished man, not severely ill. The blood count, urine examination and Wassermann reaction were all normal.

There was a uniform redness on the sides and front of the neck and patches of redness and scaling on the sides of the face, the bridge of the nose and forehead, the upper part of the chest and the upper extremities, mainly the external surfaces, as well as a few spots on the front of the legs. The ears were involved, but the back of the neck was comparatively free. There was no atrophy or telangiectasia, the areas being macular to slightly raised.

**Treatment**—Treatment consisted of strong solution of iodine U S P administered perorally, 3 drops three times a day increased gradually to 9 drops three times a day along with crude liver extract. Use of strong solution of iodine was finally discontinued because a slight swelling of the lymph nodes of the neck developed together with some dryness in the mouth and throat. Three drops of 5 per cent tincture of iodine was

then given by mouth three times a day, this treatment continuing over a period of eight months. Improvement was gradual and continuous. The patient was discharged four months ago, entirely free from all lesions. Only pigmentation and depigmentation remained.

The patient was seen again on June 7, 1944, having in the meantime been across the equator and exposed to strong heat and sunlight without experiencing any recurrence of the redness and swelling of his skin, the first time since its onset in 1934 that exposure to the sun's rays had not resulted in an exacerbation of the eruption. On the left side of the neck there was a red, discrete split pea-sized papular and scaly eruption covering an area 5 cm in diameter, of one month's duration. There were deeply tanned and leukodermic areas on the face, cheek, chest, back and extremities at the sites of former lesions. The patient feels definitely that the treatment has proved beneficial.

#### COMMENT

Three of the 5 patients with generalized lupus erythematosus had severe constitutional symptoms of a grave nature. The cutaneous lesions were widely distributed and severe, though of secondary importance.

The remaining 2 patients also had generalized cutaneous lesions of the same character, but 1 had no constitutional symptoms, and the other complained only of fatigue, weakness and shortness of breath. Neither was really ill.

All 5 patients gave a history of sunburn before the outbreak of the other cutaneous lesions. Each patient had received treatment of various sorts, including vitamin therapy, injections of calcium, bismuth and gold preparations and sulfanilamide, prior to coming under my observation.

Under my care each patient was given strong solution of iodine U S P in doses of 3 drops three times daily, and increased in some cases, to 20 drops three times a day, or 3 per cent tincture of iodine three times a day, beginning with 3 drops and increasing to 9 drops, depending on the patient's tolerance of the drug. Symptoms following the administration of the iodine preparations varied from the formation of a cold abscess in 1 patient to slight headaches and dryness of the mouth and throat in another.

I should like to digress here for a moment to mention an unusual reaction which I recently observed following the local application of iodine in a case of discoid lupus erythematosus. I painted an area with a 15 per cent solution of iodine for several days in succession. The patient acquired a high degree of idiosyncrasy to the drug, as was manifested by an almost unbearable throbbing headache, chiefly in the occipital region, deep redness of the face and conjunctivas, with watering of the eyes, rapid pulse and respiration and, at various times, a rise in blood pressure within a period of five minutes from 115 to 175 systolic and 100



diastolic and from 126 to 186 systolic and 110 diastolic

I saturated a piece of cotton with the iodine and held it a few inches from her nose for five minutes. The patient experienced the same symptoms previously enumerated, although in much milder form, and her blood pressure went up 25 mm

#### SUMMARY AND CONCLUSIONS

In this paper I have presented the histories of 5 patients suffering from generalized lupus erythematosus, all of whom received iodine internally, in addition to a high caloric diet, vitamins and, in 1 case, blood transfusions

Coincident with the iodine medication, there was an appreciable lessening of the constitutional symptoms and clearing of the skin

All 5 patients are now free of symptoms except 1, who has transient pains in her fingers at night. All have gained weight. The cutaneous lesions have entirely disappeared

I believe that iodine should be given a trial in all cases of disseminated lupus erythematosus in which other remedies have failed. I also feel that it is wise to build up the patient's general health by a high caloric diet, if possible one which provides 3,000 to 5,000 calories a day

371 Park Avenue

#### ABSTRACT OF DISCUSSION

DR FREDERICK R. SCHMIDT, Chicago. I am glad to hear of Dr. Cannon's beneficial results in the treatment of lupus erythematosus with iodine. Four years ago before this association I reported a series of 70 cases of cutaneous disease treated with iodine. In that paper I expressed the idea that I thought that the beneficial results obtained were due to the vasodilator effect of iodine.

Several investigators have shown that even minimal doses of iodine act to dilate the peripheral blood vessels, but I have subsequently found that different parts of these blood vessels are dilated, in other words, the effect varies on arterioles and capillaries. With work that I am doing now, I find that when histamine is injected it constricts the arterioles and causes capillary dilatation while an altogether different result is obtained from, for instance, injections of acetylcholine.

The failure to find gold in active lesions which do not respond to gold therapy may be due to the presence of arteriolar constriction and not to the capillary dilatation.

It has proved interesting to me to hear Dr. Cannon's paper along these lines. I believe that a good many of these so-called diffuse vascular diseases of the skin such as erythema nodosum, purpura, acrodermatitis atrophicans, dermatomyositis and lupus erythematosus are results of a mechanism that is intimately involved with vascular spasm.

DR. RICHARD S. WRISS, St. Louis. I must confess that Dr. Cannon's results are far better than anything I could have reported up to within a few months ago.

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The dosage was 3 minims (0.18 cc) of strong solution of iodine U. S. P. or 3 per cent tincture of iodine three times a day diluted in water or milk, before or after meals. This was increased 1 drop daily to as high as 20 drops three times a day. In most instances the dosage was not more than 9 drops three times a day. The medicine was given continuously over a period of months, 1 patient having taken it as long as nine months without intermission.

dilutions of 1 1,000,000 and 1 100,000. A culture from the throat showed no hemolytic organisms. An electrocardiogram and roentgenogram of the heart were both normal. Roentgenograms of the sinuses and of the gallbladder showed no abnormalities. Roentgenograms of the chest revealed calcifications in the left hilar and left pulmonary fields, as well as in the left cervical region. A biopsy of the skin showed some hyperkeratosis and a fairly narrow but easily discernible granular layer with atrophy of parts of the epidermis. Some of the superficial capillaries were dilated. Small foci of lymphocytic infiltration were found perivascularly situated. There were similar changes about the hair follicles. A definite edema was also noted. The changes were consistent with a diagnosis of lupus erythematosus, although they were not those of a well developed case.

The patient was given 3 drops of strong solution of iodine U S P three times a day, and the right upper extremity was painted with 3 per cent tincture of iodine. Her improvement was rapid. The entire skin was almost clear when she was discharged, five weeks after admission. The arm that had been painted with 3 per cent tincture of iodine was the last part of the skin to become normal, the nonpainted portions having recovered some weeks earlier. The patient has been well for more than two years.

#### CASE 5—*Lupus erythematosus disseminatus*

Mr I L, a 47 year old, single, Swedish-American engineer on a tanker, was first seen on April 5, 1943, complaining of a widespread red scaly eruption following exposure to the tropical sun five months previously.

*Past History*—He had never been ill except for typhoid in 1912. While he was in the tropics in 1934 he sustained a bad sunburn, which left red areas over most of the exposed parts. Since then any exposure to strong sunlight has caused an acute flare-up of the eruption. He has always been well in cool climates and when his skin was protected from the sun.

*Present Illness*—The present attack began while the patient was in the tropics in December 1942, starting with a redness and burning of the parts of the body not covered by a bathing suit, so severe that it "almost drove him out of his mind." He saw several physicians, one of whom suggested the diagnosis of lupus erythematosus. Various local remedies were applied, without any benefit. He has never had any constitutional symptoms, except for a feeling of fatigue and some irritability from the local discomfort.

*Examination*—Physical examination revealed a well developed and well nourished man, not severely ill. The blood count, urine examination and Wassermann reaction were all normal.

There was a uniform redness on the sides and front of the neck, and patches of redness and scaling on the sides of the face, the bridge of the nose and forehead, the upper part of the chest and the upper extremities, mainly the external surfaces, as well as a few spots on the front of the legs. The ears were involved, but the back of the neck was comparatively free. There was no atrophy or telangiectasia, the areas being macular to slightly raised.

*Treatment*—Treatment consisted of strong solution of iodine U S P administered perorally, 3 drops three times a day increased gradually to 9 drops three times a day, along with crude liver extract. Use of strong solution of iodine was finally discontinued because a slight swelling of the lymph nodes of the neck developed, together with some dryness in the mouth and throat. Three drops of 5 per cent tincture of iodine was

then given by mouth three times a day, this treatment continuing over a period of eight months. Improvement was gradual and continuous. The patient was discharged four months ago, entirely free from all lesions. Only pigmentation and depigmentation remained.

The patient was seen again on June 7, 1944, having in the meantime been across the equator and exposed to strong light and sunlight without experiencing any recurrence of the redness and swelling of his skin, the first time since its onset in 1934 that exposure to the sun's rays had not resulted in an exacerbation of the eruption. On the left side of the neck there was a red, discrete split pea-sized papular and scaly eruption covering an area 5 cm in diameter, of one month's duration. There were deeply tanned and leukodermic areas on the face, cheek, chest, back and extremities at the sites of former lesions. The patient feels definitely that the treatment has proved beneficial.

#### COMMENT

Three of the 5 patients with generalized lupus erythematosus had severe constitutional symptoms of a grave nature. The cutaneous lesions were widely distributed and severe, though of secondary importance.

The remaining 2 patients also had generalized cutaneous lesions of the same character, but 1 had no constitutional symptoms, and the other complained only of fatigue, weakness and shortness of breath. Neither was really ill.

All 5 patients gave a history of sunburn before the outbreak of the other cutaneous lesions. Each patient had received treatment of various sorts including vitamin therapy, injections of calcium bismuth and gold preparations and sulfanilamide, prior to coming under my observation.

Under my care each patient was given strong solution of iodine U S P in doses of 3 drops three times daily, and increased in some cases to 20 drops three times a day, or 3 per cent tincture of iodine three times a day, beginning with 3 drops and increasing to 9 drops, depending on the patient's tolerance of the drug. Symptoms following the administration of the iodine preparations varied from the formation of a cold abscess in 1 patient to slight headaches and dryness of the mouth and throat in another.

I should like to digress here for a moment to mention an unusual reaction which I recently observed following the local application of iodine in a case of discoid lupus erythematosus. I painted an area with a 15 per cent solution of iodine for several days in succession. The patient acquired a high degree of idiosyncrasy to the drug, as was manifested by an almost unbearable throbbing headache, chiefly in the occipital region, deep redness of the face and conjunctivas with watering of the eyes, rapid pulse and respiration, and, at various times, a rise in blood pressure within a period of five minutes from 115 to 175 systolic and 100

diastolic and from 126 to 186 systolic and 110 diastolic

I saturated a piece of cotton with the iodine and held it a few inches from her nose for five minutes. The patient experienced the same symptoms previously enumerated, although in much milder form, and her blood pressure went up 25 mm

#### SUMMARY AND CONCLUSIONS

In this paper I have presented the histories of 5 patients suffering from generalized lupus erythematosus, all of whom received iodine internally, in addition to a high caloric diet, vitamins and, in 1 case, blood transfusions

Coincident with the iodine medication, there was an appreciable lessening of the constitutional symptoms and clearing of the skin

All 5 patients are now free of symptoms except 1 who has transient pains in her fingers at night. All have gained weight. The cutaneous lesions have entirely disappeared

I believe that iodine should be given a trial in all cases of disseminated lupus erythematosus in which other remedies have failed. I also feel that it is wise to build up the patient's general health by a high caloric diet, if possible one which provides 3,000 to 5,000 calories a day

371 Park Avenue

#### ABSTRACT OF DISCUSSION

DR. FREDERICK R. SCHMIDT, Chicago. I am glad to hear of Dr. Cannon's beneficial results in the treatment of lupus erythematosus with iodine. Four years ago before this association I reported a series of 70 cases of cutaneous disease treated with iodine. In that paper I expressed the idea that I thought that the beneficial results obtained were due to the vasodilator effect of iodine.

Several investigators have shown that even minimal doses of iodine act to dilate the peripheral blood vessels, but I have subsequently found that different parts of these blood vessels are dilated; in other words, the effect varies on arterioles and capillaries. With work that I am doing now, I find that when histamine is injected it constricts the arterioles and causes capillary dilatation while an altogether different result is obtained from, for instance, injections of acetylcholine.

The failure to find gold in active lesions which do not respond to gold therapy may be due to the presence of arteriolar constriction and not to the capillary dilatation.

It has proved interesting to me to hear Dr. Cannon's paper along these lines. I believe that a good many of these so-called diffuse vascular diseases of the skin such as erythema nodosum, purpura, acrodermatitis atrophicans, dermatomyositis and lupus erythematosus are results of a mechanism that is intimately involved with vascular spasm.

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# ACRODERMATITIS ATROPHICANS CHRONICA

HAMILTON MONIGOMERY, M.D.<sup>1</sup>

AND

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Many names have been given to the disease considered in the present paper, which in the United States is most commonly referred to as acrodermatitis chronica atrophicans<sup>1</sup> but which when generalized also is called diffuse idiopathic atrophy of the skin. Other terms include "dermatitis atrophicans diffusa progressiva" (Oppenheim), *dermatite chronique atrophante* (*maladie de Pick-Herxheimer*) and the older term *erythromyelia* (Pick). The disease is not to be confused with types of atrophoderma maculatum (*atrophia maculosa et striata*<sup>2</sup>) or macular atrophies, including forms of anetoderma,<sup>3</sup> or *vegetines*, and *striae distensae*. The terms "idiopathic macular atrophy," "anetoderma maculosum" or "anetoderma erythematodes" of Jadassohn, "dermatitis atrophicans maculosa" and *vegetines* are all applied to discrete, macular, atrophic lesions which may be associated with acrodermatitis chronica atrophicans, occur entirely independent of the latter disease or arise secondarily from other dermatoses.

We wish to report our observations in 45 cases of acrodermatitis chronica atrophicans encountered at the Mayo Clinic up to January 1944, in 20 of which one or more specimens were removed for biopsy. Emphasis will be placed on the histo-

pathologic characteristics which we believe to be distinctive and specific in the majority of the cases. Acrodermatitis chronica atrophicans has been reviewed thoroughly by Oppenheim,<sup>4</sup> by Petges,<sup>5</sup> by Pautrier and his co-workers<sup>6</sup> and in the United States especially by Wise<sup>7</sup> and, more recently, by Sweitzer and Laymon.<sup>8</sup> We are essentially in accord with the opinions expressed in these reviews, which vary from one another only in certain points. One of us (R. R. S.) abstracted the literature including

4 Oppenheim, M. Atrophien, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin Julius Springer, 1931, vol 7, pt 2, p 500.

5 Petges, G. Dermatite chronique atrophante (*maladie de Pick-Herxheimer*), in Drier, J. and others. Nouvelle pratique dermatologique. Paris: Masson & Cie, 1936, pp 69-94.

6 (a) Pautrier, L. M., and Elsascheff, O. Contribution a l'etude de la dermatite chronique atrophique (*Erythromelie de Pick*) (*Acrodermatitis chronica atrophicans de Herxheimer*), Ann de dermat et syph 2 241-256 (June) 1921. (b) Elsascheff, O. Dermatite chronique atrophique (*acrodermatitis chronica atrophicans de Herxheimer*) avec lesions sclerodermiques, in Tirage a part du deuxieme Congres des dermatologistes et syphiligraphes de langue française, Strasbourg, July 25-27, 1923, pp 591-596. (c) Sloimovici, A. La dermatite chronique atrophante, Thesis, Les Editions Universitaires de Strasbourg, 1928, pp 1-111. (d) Pautrier, L. M., and Diss, A. L'anatomie pathologique de la dermatite chronique atrophante de Pick-Herxheimer, Bull Soc franç de dermat et syph 36 785-792 (May 26) 1929, (e) Histopathologie de l'anetoderme, ibid 36 815-817 (May 26) 1929. (f) Pautrier, L. M. Les rapports de la dermatite chronique atrophante, de l'anetoderme et de la scleroderme. L'etude des troubles du metabolisme du tissu conjonctif, ibid 36 973-978 (May 26) 1929.

7 (a) Wise, F. Acrodermatitis Chronica Atrophicans and Its Relation to Scleroderma, New York M J 118 73-80 (July 18) 1923, (b) Acrodermatitis Chronica Atrophicans. The Transition from Infiltration to Atrophy, J Cutan Dis 32 295-308 (April) 1914, (c) The Differential Diagnosis Between Acrodermatitis Chronica Atrophicans and Diffuse Idiopathic Atrophy of the Skin. A Clinical Study, Arch Diagnosis 8 33-42 (Jan) 1915. (d) Wise, F., and Snyder, E. J. Acrodermatitis Chronica Atrophicans. Its Symptomatology and Diagnosis, Am J M Sc 149 508-523 (April) 1915.

8 Sweitzer, S. E., and Laymon, C. W. Acrodermatitis Chronica Atrophicans, Arch Dermat & Syph 31 196-212 (Feb) 1935.

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1 The term acrodermatitis atrophicans chronica is given in the "Standard nomenclature of disease" (Jordan, E. P. Standard Nomenclature of Disease and Standard Nomenclature of Operations, Chicago, American Medical Association, 1942). We prefer the term acrodermatitis chronica atrophicans on the basis of more common usage, the predominant chronicity of the disease and the fact that atrophic changes do not always predominate.

2 Ormsby, O. S., and Montgomery, H. Diseases of the Skin, ed 6, Philadelphia, Lea & Febiger, 1943, pp 585-613.

3 Jadassohn, J. Atrophien der Haut, in Dermatologie, Vienna, Weidmann & Co., 1938, chap 4, pp 281-290.

reports of cases up to 1936, and the other (H M) has done the same thing for the literature up to 1944. It is impractical, short of a monograph, to acknowledge all important observations, for most of which the reader is referred to the reviews previously mentioned. Our remarks, therefore, are based on the correlation of multiple concepts and interpretations of what makes up acrodermatitis chronica atrophicans to be found in the literature, together with our own observations in this series of cases.

jective symptoms such as pruritus are usually minimal but may occasionally be severe. Most of the associated phenomena and variations of the disease will be mentioned in the following analysis of our cases without attempting a detailed description of these phenomena, which are well described in various treatises. Thirty-seven of the patients who had acrodermatitis chronica atrophicans were women, and only 8 were men. This is a considerably higher proportion of women than in other series previ-



Fig 1—Acrodermatitis chronica atrophicans. (a) Knee of a woman aged 45 years who had generalized involvement of five years' duration. (b) Lesions of a year's duration on leg of a woman aged 70 years who had stasis ulcers for twenty-two years. Note the pseudosclerodermatous changes on the ankle and superficial ulcers. Lesions also occurred on the other leg and on the arms.

#### CLINICAL OBSERVATIONS

Acrodermatitis chronica atrophicans may be defined as a chronic progressive form of dermatitis of unknown cause involving primarily the extremities (limbs) and characterized by a bluish red, thin, atrophic, tissue-paper-like wrinkled skin, resulting from atrophy of the epidermis or more especially of the cutis, so that the deeper vessels become readily visible (figures 1 to 4, in all of which except figures 2c and 2d the diagnosis was confirmed histopathologically).

ously reported.<sup>9</sup> Six of the 45 patients were born in the United States, for the most part of native-born parents. Eight patients were of Scandinavian birth, and 1 was a Mexican, making 15 of the 45 who were born outside of the central land mass of the European continent and Russia. Fifteen of our patients stated that they were Jewish. Acrodermatitis chronica

<sup>9</sup> Jordan, A. Ueber die Aetiologie der idiopathischen progressiven Hautatrophie (Acrodermatitis chr Atrophicans), Russk. klin. 12.801-822, 1929, abstracted, Zentralbl. f. Haut- u. Geschlechtskr. 34 312, 1930.

atrophicans has recently been reported in natives of South America,<sup>10</sup> Greece<sup>11</sup> and Turkey<sup>12</sup> as well as in a number of patients born in the United States. This disease, therefore, is not limited to one nationality or continent and occurs fairly frequently among native-born Americans.<sup>13</sup>

A familial history of the disease has occasionally been reported<sup>14</sup> but was not encountered in this series of cases. The occupations of the patients in our series and other series were manifold and seemed to have no relation to the disease.



Fig 2—Aerodermatitis chronica atrophicans (a and b) Typical changes of two years' duration, limited to both extremities. The patient was a woman aged 59 years. Note the branny scaling and pseudosclerodermatous changes on the ankles, which are independent of varicosities as shown in b, photographed with infra-red rays (c). Lesions limited to both arms of a woman aged 34 years. Note the ulnar band and deep-seated nodular infiltrations erroneously diagnosed previously as erythema nodosum. (d) Photograph made with infra-red rays in same case as in c.

10 Piantoni, C, and Ferraris, A. Dermatitis atrophicans chronica Pick-Herxheimer, *Rev argent dermatosif* **22** 272, 1938.

11 Photinos, M P. Un cas d'aerodermatite chronique atrophique de Pick-Herxheimer, *Bull Soc franç de dermat et syph* **44** 1070 (June 10) 1937.

12 Erel, N O. Ueber einen Fall von Dermatitis chronica atrophicans Pick-Herxheimer, *Bull Soc turq med*, 1937, no 1, abstracted, *Zentralbl f Haut- u Geschlechtskr* **56** 37, 1937.

13 Michelson, H E. Acrodermatitis Chronica Atrophicans, *Arch Dermat & Syph* **38** 650 (Oct) 1938. Sullivan, R R, in discussion on Michelson O'Leary, P A, Montgomery, H, and Brunsting, L A. Acrodermatitis Chronica Atrophicans, *ibid* **41** 750 (April) 1940. Sullivan, R R, in discussion on O'Leary, Montgomery and Brunsting.

The age of the patient at the time of examination in our cases varied from 22 to 89 years, with an average of 53 years. The duration of the disease at the time of examination varied from three months for a woman aged 50 years to more than half a century for a woman aged 57 years in whom the disease had been present since early childhood. The average duration was thirteen years. The age of the patient at time of onset of the disease varied from about 7 to 87 years, with an average age of 40 years.

14 Director, W, and Bluefarb, S M. Familial Occurrence of Acrodermatitis Atrophicans Chronica. Report of Two Cases, *Arch Dermat & Syph* **46** 480-482 (Oct) 1942.

In conformity with previous reports, the disease tended to begin on the legs or arms, especially on the extensor surfaces, in relation to the joints, such as the elbows, knees, wrists and ankles. The disease started on the legs, ankles or feet in 33 cases and on the elbows or hands in 10. In 1 case from the beginning there was a generalized involvement of the body, in 1 case the site of onset was not known. Wise, Oppenheim and others have described the earliest changes as edematous, soft, bluish red, boggy or doughy tumors, which according to Wise have

Several others of our patients gave a history of a diffuse edema of one or more extremities or of redness and diffuse swelling preceding any atrophic changes. In 1 case, there was a peculiar fusiform swelling of the wrists and the proximal phalanges of the first three fingers of both hands with limitation of motion apparently due to juxta-articular swelling but without changes discernible on roentgenologic examination or evidence of arthritis.

A history of trauma preceding the onset of the disease was given in only a few cases. In none



Fig 3—Acrodermatitis chronica atrophicans race. The patient was a woman aged 48 years presented at a meeting of the New York Dermatological Society in December 1943, by Dr J C Graham. At that time all the members present, including Dr Wise, concurred in the diagnosis of generalized idiopathic atrophy.)

Generalized involvement of three years' duration, including the face. There were some features of poikiloderma. (This patient was presented at a meeting of the New York Dermatological Society in December 1943, by Dr J C Graham. At that time all the members present, including Dr Wise, concurred in the diagnosis of generalized idiopathic atrophy.)

been confused with the edematous phases of scleroderma, scleredema and allied conditions. We did not have the opportunity to see these early manifestations nor were they described in more than 1 of our cases. In this case the patient, an Austrian woman cook, aged 34 years, who had had acrodermatitis chronica atrophicans for ten years limited to both arms (fig 2c and d), had been seen at the clinic almost ten years earlier in which time a diagnosis had been made of erythema nodosum limited to both arms and of a month's duration. In retrospect we believe this was the beginning of the acrodermatitis

of the cases in this series could the onset or course of the disease be attributed to changes of temperature either from exposure to the elements or as the result of the patient's occupation. In regard to distribution of the lesions, the legs were involved in 23 cases, the ankles or feet in 5, the legs and arms in 14 and the arms alone in 3. In 3 cases the lesions were unilateral, being limited in 1 case to one leg and in 2 cases to one arm, there was no serologic or clinical evidence of syphilis in these cases. The trunk and extremities were involved in 6 cases, in 2 of which

there also was involvement of the face (fig 3). In 3 of the 6 cases with involvement of the trunk there was generalized erythroderma, in 1 case with features of poikiloderma (fig 3). Patchy alopecia of the scalp was also seen in this case. Bullae, generalized pigmentation or vitiligo did not occur in any case in this series. In 1 case there was lichenification of the labia but without atrophy. In none of the cases was there evidence of atrophy or other involvement of any of the mucous membranes such as has been reported by Swetzer and Laymon and others. The palms and soles were not involved except in 1 case,

seen extending along the radius or, less frequently, from the knee down the tibia.

Fibrous nodules (fig 4a), which usually tend to be multiple and may be of the color of the skin or yellowish, occurred about the elbows or along the ulna in 4 of our cases. Because of their location over joints, they have been confused with juxta-articular and rheumatic nodules and, because of the color, with xanthoma. Typical lesions of xanthoma as reported by Jessner<sup>16</sup> were not demonstrable, and the blood plasma lipids in 2 of the cases were normal. In 1 case (fig 4a) there was no evidence on histochemical

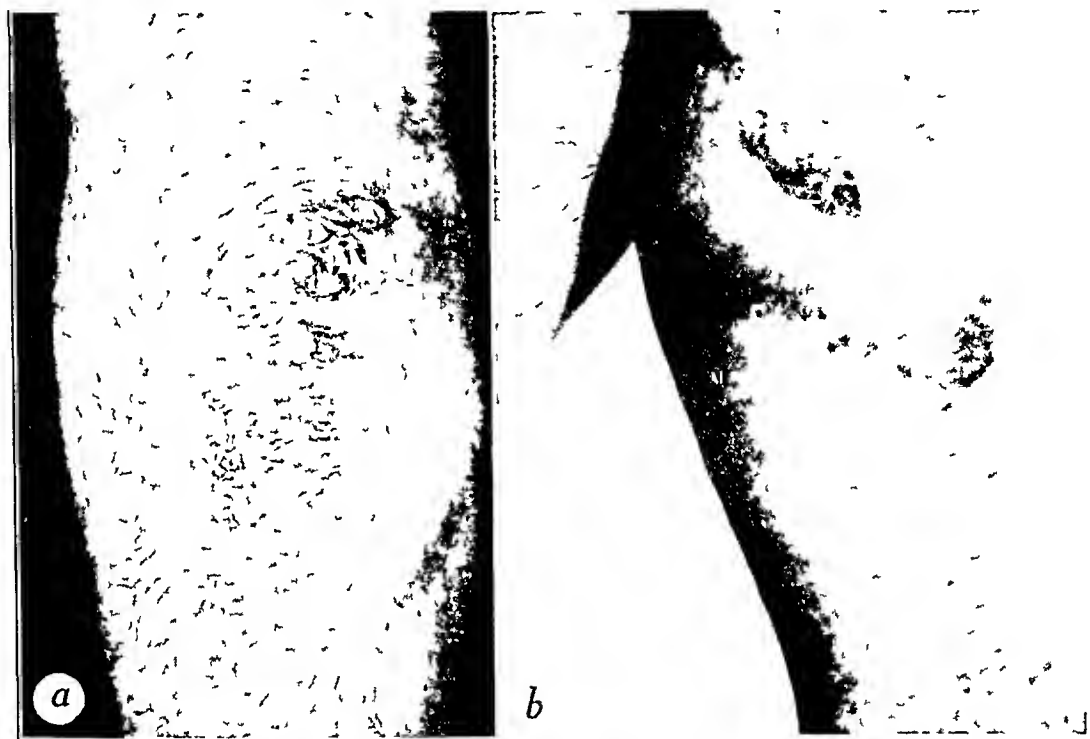


Fig 4—(a) Fibrous nodules of ten years' duration on the elbows associated with acrodermatitis of the limbs of seven years' duration. The patient was a man aged 57 years who had old, treated latent syphilis and also arteriosclerosis obliterans of the lower extremities of two years' duration. (b) Acrodermatitis chronica atrophicans of three years' duration, with dark areas of amyloidosis on the leg. The patient was a woman aged 44 years.

in which there was slight involvement of the plantar surface of one foot. In none of the 45 cases were the tips of the fingers or toes involved in the process.<sup>15</sup> Changes in the nails also were minimal and could not be attributed directly to the disease.

Varying degrees of so-called ulnar bands were encountered in 9 of the 45 cases (fig 2c and d). These occurred as bands of infiltration, edema and fibrosis or later as atrophy extending along the ulnar to the wrist joint. The bands were also

<sup>15</sup> Oppenheim<sup>4</sup> was correct, therefore, in criticizing the term "acro" as applied to this disease if one limits this term to involvement of the digits (tips of the extremities) rather than accepting its broader use as involving the extremities (limbs).

or histopathologic analysis of increase of tissue lipids. According to Oppenheim<sup>17</sup> lipomas or lipomatous masses above an area of acrodermatitis are of fairly frequent occurrence, but none were seen in this series.

Pseudosclerodermatous changes were encountered in 17 of the 45 cases, in most instances

<sup>16</sup> (a) Jessner, M. Weiterer Beitrag zur Kenntnis der Acrodermatitis chronica atrophicans, *Arch f Dermat u Syph* **139** 294-305, 1922, (b) Zur Kenntnis der Akrodermatitis chronica atrophicans, *ibid* **134** 478-487, 1921. (c) Jessner, M., and Loewenstamm, A. Bericht über 66 Fälle von Acrodermatitis chronica atrophicans, *Dermat Wehnschr* **79** 1169-1177 (Oct) 1924.

<sup>17</sup> Ebert, M. H. Acrodermatitis Chronica Atrophicans, *Arch Dermat & Syph* **42** 1147 (Dec) 1940. Rothman, S., Zeisler, E. P., and Oppenheim, M., in discussion on Ebert.

being limited to the legs, ankles and feet. They occurred as ill defined, brawny, infiltrated bands and plaques often associated with a branny or flaky scale (figs 1 *b* and 2). Occasionally the skin of the entire leg was reddened and tense rather than lax and wrinkled, apparently as a result of edematous rather than true sclerodermatous changes. One patient had pseudosclerodermatous bands on the trunk. In none of the cases were there lesions of morphea or the distinct, sharply defined, linear bands of localized scleroderma, and in none was there evidence of acrosclerosis, sclerodactylia or Raynaud's disease.

Ulcers of various types were encountered in 14 cases and occurred chiefly on the lower extremities, especially about the ankles and especially in pseudosclerodermatous areas (fig 1 *b*). In 6 of these cases, there was a history of varicose or stasis ulcers of the lower extremities preceding the acrodermatitis chronica atrophicans by a good many years. In all of the 6 cases there was definite evidence of incompetent venous circulation. In other cases in which ulcers occurred there was no evidence of venous incompetency. Photographs with infra-red rays in several cases did not reveal any relation of the superficial veins to the ulcers or to the ulnar bands or areas of pseudoscleroderma (fig 2). Ulceration, as a rule, did not occur in atrophic areas. In 1 case, however, in which there was generalized acrodermatitis (fig 3) multiple small bluish red, purpuric, hemorrhagic lesions were scattered over the trunk. These lesions broke down into indolent ulcers up to 1 cm in diameter which healed slowly. Oppenheim<sup>4</sup> (his figure 27, page 584) described a case in which there were impetiginous ulcers of the ankles and legs from which staphylococci were isolated on culture and which to a certain extent resembled small gummas.

In only 1 case of acrodermatitis were there associated lesions of macular atrophy, a much smaller incidence of association of these two diseases than in other series reported in the literature. In 1 of our cases there was localized amyloidosis (fig 4 *b*). In 1 case acrodermatitis was associated with long-standing eczema, probably atopic. A few cases associated with psoriasis<sup>18</sup> have been reported but without relation to the psoriasis, and this applies to lichen planus<sup>6</sup> and rare combinations of acrodermatitis chronica atrophicans with dermatitis herpetiformis, erythrocytosis, lupus erythematosus,

Hodgkin's disease,<sup>19</sup> ichthyosis, herpes zoster and livedo racemosa as reported by Oppenheim.

In regard to systemic disease, there were only 12 in our series of 45 in which there was evidence of cardiovascular disease. Only 4 patients had any degree of arteriosclerosis. Four others had hypertension, 3 had definite cardiac disease, and 1 had arteriosclerosis obliterans. This patient had a moderate elevation of plasma lipids, but this is common in the disease. In all but 2 of these 12 cases the cardiovascular involvement had begun in the later decades of life and without definite relation to the acrodermatitis chronica atrophicans. The results of vascular studies, including capillary studies in several of the cases, were essentially negative.<sup>20</sup>

Varying degrees of arthralgia or mild arthritis occurred in 7 of the 45 cases. In none, however, was there arthritis deformans such as Sweitzer and Laymon<sup>8</sup> have described, and in none of many cases studied roentgenologically were there atrophic roentgenologic changes in the bones as described by Jessner and Loewenstamm<sup>16c</sup> in 10 of 17 cases. The symptoms of arthritis in some cases appeared before the cutaneous lesions. Foci of infection were present in only a few cases. The same was true in regard to anemia or thyroid dysfunction.

No definite relation of the disease to the menopause or to ovarian dysfunction could be established, despite the predominance of women more than 40 years of age in the series. Systemic disease appears to be coincidental or at most a secondarily associated phenomenon of acrodermatitis chronica atrophicans.

#### HISTOPATHOLOGY

There is a lack of agreement in regard to the significant histopathologic changes in acrodermatitis chronica atrophicans.<sup>21</sup> This can be explained from the fact that the microscopic

19 Andrews. Acrodermatitis Chronica Atrophicans and Hodgkin's Disease, Arch Dermat & Syph **16**:474 (Oct) 1927. This case was not accepted as an instance of acrodermatitis chronica atrophicans by most of the persons present.

20 Pautrier, L. M., and Ullmo, A. Note sur la capillaroscopie de la dermatitis chronique atrophique et de la sclerodermie, Bull Soc franç de dermat et syph **36** 776-780 (May 26) 1929.

21 (a) Kyrle, J. Atrophie der Haut, in Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen, Berlin, Julius Springer, 1925, vol 1, pp 121-153. (b) McCarthy, L. The Atrophies of the Skin, in Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931, chap 3, pp 58-92. (c) Gans, O. Die Atrophien der Haut, in Histologie der Hautkrankheiten, Berlin, Julius Springer, 1925, vol 1, pt 1, chap 3, pp 12-46. (d) Oppenheim<sup>4</sup>. (e) Petges<sup>5</sup>. (f) Pautrier and Diss<sup>6a</sup>. Wise<sup>7a</sup>. Jessner<sup>16a, b</sup>.

18 Pautrier, L. M., and Woringer, F. Psoriasis signe sur le corps avec lesions des membres inferieurs developpees au niveau d'un Pick-Herxheimer, Bull Soc franç de dermat et syph **45** 1315-1316 (July 10) 1938.



changes vary considerably depending on the stage of the disease and on the location of the region from which tissue is taken for biopsy, including whether there were associated fibrous nodules or pseudosclerodermatous changes. Furthermore, it must be borne in mind that from the histopatho-

gically not only in different cases but in different areas in the same case. We shall review the multiple changes to be seen in the disease and then briefly emphasize the histopathologic changes which we believe to be diagnostic (figs 5 to 7).

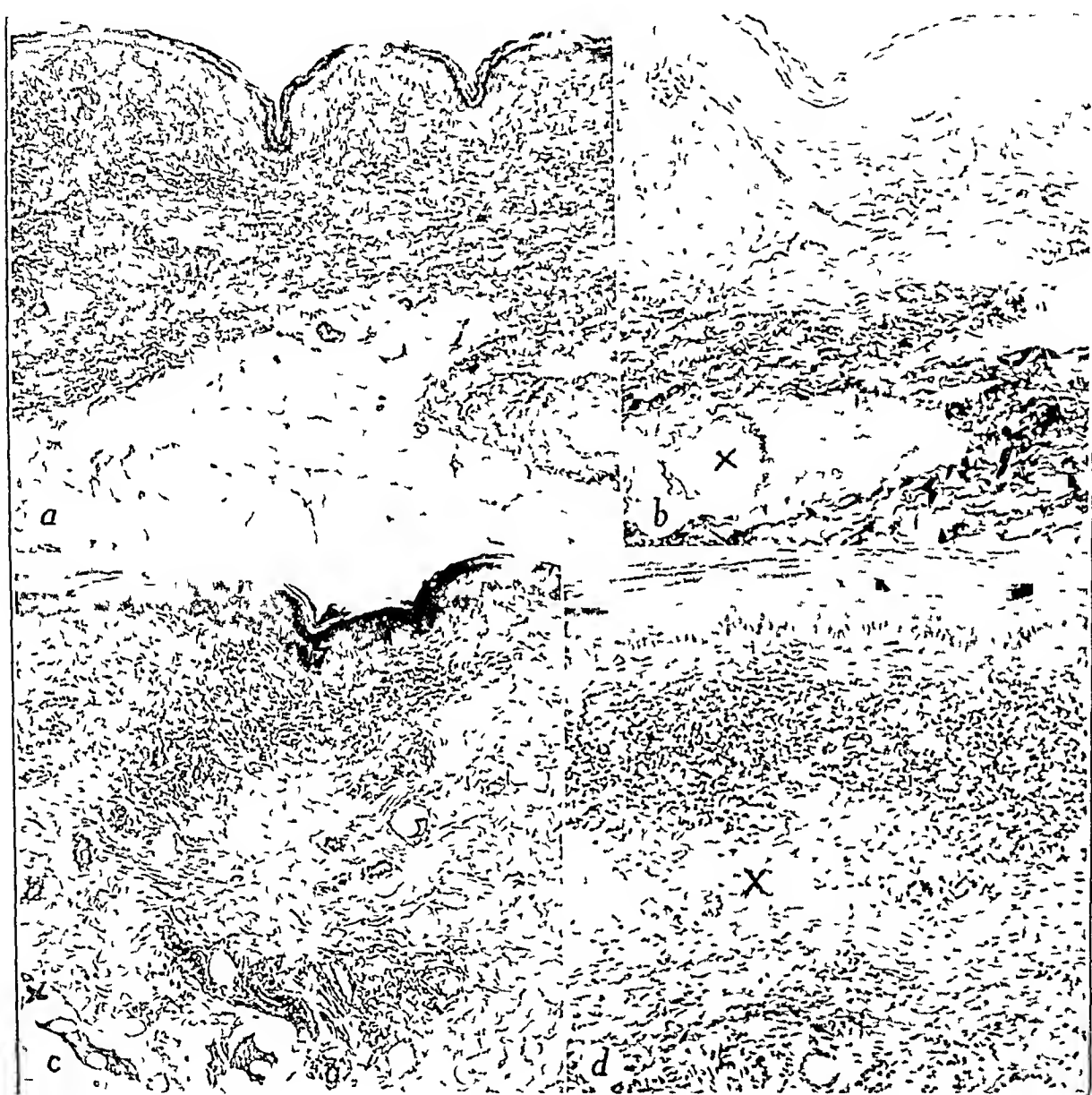


Fig 5—Acrodermatitis chronica atrophicans. (a) A section from the leg, typical atrophic epidermis with border zone and then infiltrate and atrophy of the cutis and dermal appendages ( $\times 40$ ). (b) Same case, note the preservation of fine elastic fibrils near the epidermis, destruction of elastic tissue where infiltrate occurs and involvement of a vessel at X ( $\times 115$ ). (c) Same case as figure 3, section from the arm. Note the fat replacement atrophy in the cutis and similar involvement of arrectores pilorum muscles at X ( $\times 50$ ). (d) Section from the hand, typical changes with distinct border zone but also senile cutaneous changes with bluish-staining collagen fibers at X ( $\times 100$ ).

logic descriptions many of the older reports of this disease did not belong with the reports of acrodermatitis but with those of one of the other atrophic dermatoses. The histopathologic changes usually have been divided into acute, inflammatory and atrophic stages, but these are not clearcut, and the duration of any stage varies

The earlier acute phases of this disease as described by Gans,<sup>10</sup> Kyle,<sup>21a</sup> Oppenheim<sup>1</sup> and others include an early inflammatory and often edematous stage, in which there is a perivascular inflammatory reaction in the cutis without alteration of the epidermis. The rete ridges are well preserved, and the stratum corneum usually



shows no change. Exceptionally, there is slight parakeratosis. Gans, Kyrle, Oppenheim and others explain the doughy infiltrations seen clinically on the basis of transitory edematous changes in the cutis, which could account for transient parakeratosis. Parakeratosis is not

biopsy taken until the disease had been present for a year. A biopsy of a typical lesion of a year's duration over the elbow of a woman aged 70 revealed extensive edema throughout the cutis but already showed typical histologic changes of acrodermatitis chronica atrophicans (fig 6a)

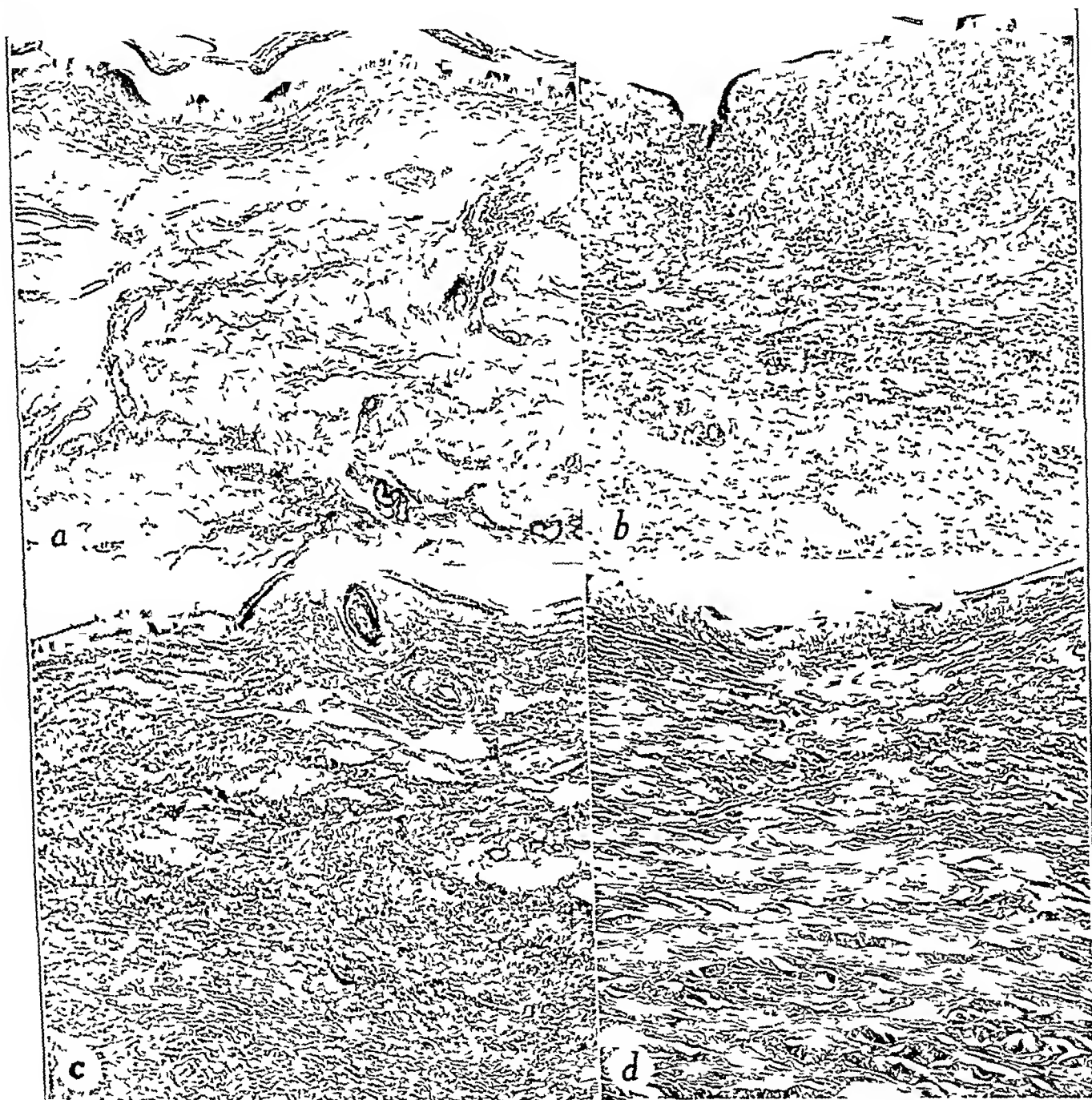


Fig 6—Acrodermatitis chronica atrophicans (a) Same case as figure 1b but from elbow. Early acute edematous stage of one year's duration, very narrow border zone between the infiltrate in the upper layer of the cutis and the atrophied epidermis ( $\times 40$ ). (b) Right knee in a case of unilateral involvement of thirteen years' duration. Note the persistence of the intense inflammatory reaction with imperfect border zone but preservation of the granular layer ( $\times 70$ ). (c) Same case and site as figure 4a. Typical changes in the epidermis and the upper layer of the cutis and a dense fibrous nodule deeper in the cutis ( $\times 26$ ). (d) From a pseudosclerodermatous band in the right breast. Note the extreme fibrosis but also the atrophy of the epidermis. The patient had generalized involvement of six years' duration starting on the feet. Typical ulnar bands are also present ( $\times 50$ ).

present in later stages of the disease. The infiltrate in the beginning is composed of a multiplicity of types of cells. The elastic and connective tissues are unaltered. There is no diminution of the thickness of the cutis nor is there any atrophy of the dermal appendages. In none of our series of cases were specimens for

Edema may persist histologically for many years, even decades, after the onset of the disease.

Within a few months at the most, histologic changes more characteristic of the disease make their appearance. There is relative to absolute hyperkeratosis but no parakeratosis. The granular layer is usually present but is thinned. Vary-

ing degrees of atrophy of the prickle cell layer are encountered. The cells may be flattened, and the intracellular bridges may become indistinct. There is also flattening of the basal cells, which may contain varying amounts of melanin pigment. Occasionally there is a mild degree of intracellular edema with vacuolar changes in the basal and the prickle cells. The rete ridges have become flattened and have disappeared, so that the epidermis stretches out as a thin, flat ribbon with varying degrees of undulations or waves which represent the lines of cleavage of the skin.

Just beneath the epidermis there is a border zone of connective tissue separating a band of infiltrate which lies beneath it from the epidermis. This border zone may be very narrow and composed of a few slender strands of connective tissue fibers running parallel to the epidermis, or there may be a wide zone, several times the thickness of the epidermis. In the beginning, the collagen fibers are distinct. Later there are homogenization and hyaline-like changes, so that the fibers merge. Even though the band of infiltrate beneath the border zone is dense, the cells of the infiltrate rarely penetrate through the border zone of connective tissue to invade the epidermis and result in early liquefactive degeneration of the basal cell layer (fig 6b). This happens in about 10 per cent of the cases, but, even when such changes are seen, stains for connective tissue reveal that the collagen fibers have been thinned and pushed apart but have not been completely destroyed. Fine fibrils of elastic tissue are found in the border zone arranged in loops perpendicular to the epidermis, which suggests that they are remnants of the elastic fibrils normally present in the papillary bodies (fig 5b). These elastic fibrils lie in close proximity to the epidermis and are not separated from the flattened epidermis by a zone of edema, such as occurs in lichen sclerosus et atrophicus. These fine elastic fibrils tend to persist in the border zone for many years, but, as a rule, they disappear, when homogenization and hyaline changes occur in the connective tissue.

There is a dense band of infiltrate beneath the border zone of connective tissue. The infiltrate in the beginning, according to Gans,<sup>22</sup> is limited chiefly to the upper layer of the cutis but later may extend throughout the cutis and subcutaneous tissue. The infiltrate is essentially perivascular and therefore also occurs about the dermal appendages and the larger vessels in the subcutaneous tissue. From the beginning, the infiltrate is composed chiefly of mononuclear cells, especially lymphocytes, and of fixed connective tissue cells, including histiocytes or reticulum cells, the latter of which may pre-

dominate over the lymphocytes. Few polymorphonuclear leukocytes or eosinophils are seen. In some cases there are varying numbers of chromatophores laden with melanin or hemosiderin pigment. In our experience, which is contrary to that of some European authors, plasma cells did not predominate nor did mast cells occur frequently. We did not observe giant cells or histologic evidence of tuberculosis, including the formation of tubercles, in any of our cases. Histologic evidence of leprosy or syphilis was also absent.

There is a gradual wasting away of the connective tissue fibers where the infiltration occurs. The collagen fibers become homogenized and fragmented, and the number of nuclei decreases. In addition, in some cases there are islands of fat cells and fat droplets high up in the cutis, near the epidermis, which seem to result from fatty degeneration of collagen fibers rather than to represent an invasion of fat cells from the subcutaneous tissue (fig 5c). It is not clear just how this degeneration of the collagen fibers takes place. The change seems to be abrupt. One rarely encounters alteration of the staining qualities of the connective tissue fibers or their merging with elastic fibers, such as occur in so-called senile skin.<sup>23</sup> This phenomenon occurred in only 1 case, the patient was a woman aged 75 who showed senile cutaneous changes in the biopsy specimen from the hand (fig 5d) but failed to show such changes in two other specimens taken from covered portions of the body. The atrophy of the collagen fibers results in a decrease of the cutis to a half or a quarter of its normal thickness. Atrophy of the cutis, however, may not occur until the disease has been present for many years, the degree of atrophy being dependent apparently on the extent and persistence of the infiltrate.

The elastic tissue, like the collagen, is destroyed where the infiltration occurs, and again the change is abrupt. The same is true in regard to destruction of *Gitterfasern* (lattice, or reticulum, fibers). The intensity of the infiltrate tends to decrease as the process becomes older, but, even in lesions of several decades' duration which clinically show atrophy without inflammation, one nevertheless finds a definite band of infiltrate beneath the border zone of connective tissue. As the infiltrate decreases, there is evidence in some cases of an apparent attempt at regeneration of the elastic fibers, and this also has been observed by Gans, Kyrle and Oppenheim. Thin, fine,

22 Hill, W. R., and Montgomery, H. Regional Changes and Changes Caused by Age in the Normal Skin. A Histologic Study, *J. Invest. Dermat.* 3: 231-245 (June) 1940.

wavy elastic fibrils appear both above and below the band of infiltrate. These are similar to the apparent new formation of elastic fibers seen in *striae cutis distensae*.

The dermal appendages are surrounded by the infiltrate. Early in the disease there are atrophy and disappearance of the sebaceous glands, and later the same is true in regard to the hair follicles. The arrectores pilorum muscles may also be invaded by cells of the infiltrate and present varying degrees of atrophy. Occasionally, however, these muscles appear to be hypertrophied and to lie parallel to the epidermis.

glands are thinned and their lumens are dilated and cystic, possibly secondary to obstructive phenomena in the ducts. The elastic tissue in the propria of the sweat glands is usually preserved. Although the bundles of cutaneous nerves are frequently surrounded by an infiltrate, no degenerative or atrophic changes have been apparent. Pautrier and Diss<sup>22</sup> are the only authors to report a case in which there were definite changes in the cutaneous nerves. When a dermal appendage is atrophied but not destroyed, there eventuates a mild degree of fibrosis about the atrophied appendage.

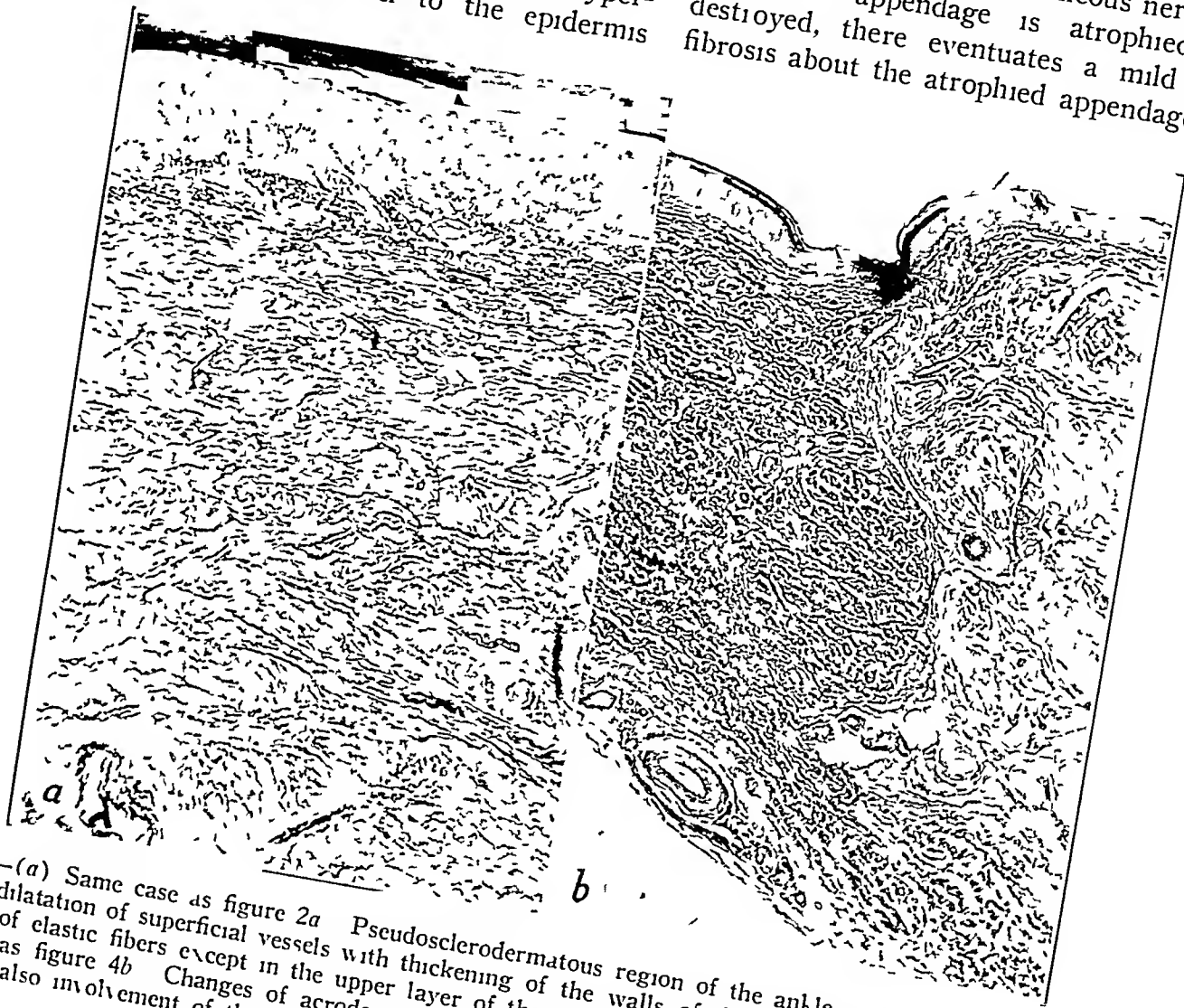


Fig 7—(a) Same case as figure 2a. Pseudosclerodermatous region of the ankle with some thickening of the epidermis, dilatation of superficial vessels with thickening of the walls of deeper vessel at X, fragmentation and diminution of elastic fibers except in the upper layer of the cutis, where there is some increase ( $\times 45$ ). (b) Same case as figure 4b. Changes of acrodermatitis at the left side. At the right side are homogeneous masses of amyloid, also involvement of the walls of a blood vessel ( $\times 50$ ).

rather than in their normal oblique position. One case in which there was leiomyoma has been reported.<sup>23</sup> Destruction of the sweat ducts frequently takes place, a fact which fits in with the diminution of sweating that has frequently been observed in this disease. The sweat glands may be intact and well preserved, but frequently they are also invaded by lymphocytes and monocytes with varying degrees of destruction of the sweat glands. In other cases, the walls of the sweat

The subcutaneous tissue usually shows decided atrophy with decrease of the size of the fat cells, varying degree of Wucher atrophy (fat replacement atrophy by invasion of the infiltrate) and a varying degree of fibrosis.

Changes in the blood vessels vary greatly, but we failed to substantiate the concept of some authors that acrodermatitis chronica atrophicans is primarily a vascular disease. In the beginning, there usually is a varying degree of dilatation of the superficial blood vessels, lymphatics and capillaries, with swelling and at times proliferation of the endothelium of the smaller vessels. A

<sup>23</sup> Smilovici, J. Ueber Kutis-Myome und Keloidbildung in Bereiche einer Akrodermatitis chronica atrophicans, Arch f Dermat u Syph 124 77-82, 1917.

perivascular infiltration frequently results in inflammatory and destructive changes in the walls of both smaller and larger vessels. Frequently, however, most of the vessels appear well preserved, without alteration of their walls and with normal elastic tissue membranes. When a specimen for biopsy is taken from the leg in cases associated with varices, one may anticipate finding evidence of varices histologically. They would appear to be coincidental findings, just as were the atheromatous changes encountered in 1 case of acrodermatitis in which there was associated arteriosclerosis obliterans. Petges<sup>5</sup> and Jessner,<sup>16a, b</sup> however, explained the varices as a result of degeneration of the elastic tissue, which deprives the vessels of their support.

Small deposits of calcium occurred in 2 of our cases but without evidence of systemic calcinosis. In 1 of our cases (fig 7b) there were deposits of an amyloid-like substance which gave weakly positive reactions to different stains for amyloid. The deposits of amyloid in this case could scarcely be attributed to injections which had been given for varicose veins. There was no evidence of systemic amyloidosis. Kenedy<sup>24</sup> reported 1 case of localized amyloidosis and referred to possibly 3 or 4 others in the literature. In searching for the cause of the atrophy of the collagen sections in many cases were stained for mucin, with negative results. The deposition of amyloid and calcium which occurred in 2 cases would seem to be a secondary degenerative phenomenon rather than of any primary etiologic significance.

In the end, or atrophic, stage of acrodermatitis there is a decided decrease of the infiltrate or it may even be absent. With the disappearance of the infiltrate, one sees simply an atrophic epidermis and cutis, the latter containing homogenized fibrotic tissue. There may be regeneration of the elastic tissue in some regions and absence of elastic fibers in others. When the elastic fibers are absent, it is problematic whether they were destroyed by the infiltrate or by toxic products of this. The histopathologic changes in this terminal stage are no longer diagnostic, any more than are the histologic characteristics of scars in most other dermatoses.

Many descriptions have been given of the histologic changes in so-called ulnar bands. Frequently the picture is that of typical acrodermatitis associated with decided edema. In other cases, fibrotic and sclerodermatous-like changes have been described. The infiltrate may be spotted

and diffuse. There may be some increase of connective tissue fibers rather than merely a swelling from edema.

The fibrous nodules (fig 4a) seen in association with acrodermatitis chronica atrophicans (fig 6a) present a histopathologic picture varying from that of subdermal fibrosis or dermatofibroma (fig 6c) or even keloid (fig 6d) to that of histiocytoma, in which deposition of hemosiderin and lipids occurs. In other cases, there is central pseudonecrosis in the nodule, so that the histopathologic changes closely simulate those seen in juxta-articular and rheumatic nodules. There was no evidence of xanthoma in any of our cases.

Regions of scaling with lichenification and induration which are often associated with pseudosclerodermatous changes—especially about the ankles—likewise show histologic changes that are not distinctive (fig 7a). There may be typical changes of acrodermatitis above a region of fibrosis or pseudoscleroderma. Frequently the sclerodermatous process extends right up to the epidermis. There may be thickening of the epidermis with hyperkeratosis, acanthosis and proliferation of the rete ridges. Thus all the pathologic characteristics of acrodermatitis become lost in these regions. There frequently are dilatation of the superficial capillaries, a region of dense fibrosis with homogenization of the connective tissue fibers and varying degrees of sclerotic changes in the deeper parts of the cutis. The infiltrate usually is more prominent than in cases of true scleroderma, but, again it may be minimal. The elastic tissue is frequently destroyed in the fibrotic and sclerodermatous regions, especially in the fibrotic nodules resembling juxta-articular nodes. In other cases, the elastic tissue is merely frayed and splintered and there may even be new formation of elastic fibers. We do not believe that a sharp distinction can be made on the basis of histopathologic observations alone between the pseudosclerodermatous plaques of acrodermatitis chronica atrophicans and true scleroderma.

The histopathologic changes in ulcers associated with acrodermatitis chronica atrophicans are not diagnostic per se and are dependent on multiple associated factors.

*Summary of Histopathologic Changes*—The histopathologic changes in acrodermatitis chronica atrophicans are, we believe, diagnostic in practically all cases if a specimen for biopsy is taken from a well developed region independent of any associated fibrous nodules, sclerodermatous changes or ulcers. The following com-

24 Kenedy, D. Ueber herdförmige Amyloidentartung bei einem Falle von Dermatitis atrophicans diffusa, Arch f Dermat u Syph **136** 245-250, 1921.



bination of changes makes a diagnostic picture. There are relative to absolute hyperkeratosis, preservation of a granular layer, atrophy and flattening of the prickle cell layer, loss of rete ridges and papillary bodies, with resultant flattening of the epidermis into a thin, wavy line and a definite border zone of normal to homogenized connective tissue between the epidermis and the infiltrate in the cutis. The infiltrate appears as a narrow or wide band beneath the border zone. There is destruction of connective and elastic tissue in this region, with pronounced atrophy to destruction of all the dermal appendages except, at times, the sweat glands. The cutis is definitely thinned as is also the subcutaneous tissue, so that deeper blood vessels become readily visible through the skin.

#### DIFFERENTIAL DIAGNOSIS

Acrodermatitis chronica atrophicans in its usual form involving the limbs is easily recognized clinically and presents a characteristic histopathologic picture. Cases, however, of generalized involvement occur, including diffuse generalized erythroderma and others presenting features of poikiloderma. On careful analysis of the clinical and histopathologic changes, these as well as many cases presented as cases of generalized idiopathic atrophy are definitely instances of acrodermatitis chronica atrophicans. It is in cases in which there is extensive involvement, however, that the disease has been confused with other dermatoses. For example, we excluded from our series of cases 1 which on final analysis fitted in better with cases of disseminated lupus erythematosus or possibly so-called poikiloderma and others in which the final diagnoses were respectively parapsoriasis, generalized lichen sclerosus et atrophicus, generalized atrophic lichen planus and finally unilateral scleroderma with morphea which had undergone involution. Ormsby's case of acrodermatitis chronica atrophicans,<sup>25</sup> presented first as an instance of poikiloderma and later considered by eminent dermatologists to be also a case possibly of lichen planus, lupus erythematosus or parapsoriasis variegata, illustrates the difficulties of diagnosis. Acrodermatitis in which there was unilateral involvement has been attributed in the past to *syphilis*. This could not be substantiated in our

series. Pardo-Castello<sup>26</sup> reported acrodermatitis chronica atrophicans associated with leprosy, which again can be distinguished by concomitant findings. The same applies to cases of cutaneous tuberculosis with poikiloderma-like changes.<sup>27</sup>

Oppenheim<sup>28</sup> expressed the belief that poikiloderma atrophicans vasculare of Jacobi is not a real clinical or histopathologic entity. In his opinion some cases belong with the cases of dermatitis atrophicans progressiva (acrodermatitis chronica atrophicans), others belong with cases of poikilodermatomyositis (Petges) and in a third group the disease is secondary to various dermatoses. We concur in this view. Foerster in the United States and others have for some time emphasized that in most cases poikiloderma is secondary to various dermatoses, including also the lymphoblastomas.<sup>29</sup> Gans<sup>21c</sup> described the histopathologic changes in poikiloderma as simulating those of lupus erythematosus. In poikiloderma, lupus erythematosus and lichen planus, histopathologically, there is definite liquefaction degeneration of the basal cell layer, which in itself serves to distinguish these diseases from acrodermatitis chronica atrophicans. Furthermore, in acrodermatitis there is a definite border zone between the epidermis and infiltrate and there is decided destruction of the collagen fibers.

Lichen sclerosus et atrophicus shows pronounced atrophy of the epidermis with preservation of the elastic fibrils beneath the epidermis, but the fibers are separated from the epidermis by a zone of edema and the other histopathologic changes are entirely different from those of acrodermatitis. Parapsoriasis presents an entirely different histopathologic picture. In localized scleroderma, there are usually some preservation of the rete ridges and an increase of connective tissue, but, as mentioned previously, differentiation from pseudosclerodermatous plaques of acrodermatitis chronica atrophicans may not be possible histopathologically. Wise and, more

26 Pardo-Castello, V. Leprosy Associated with Dermatitis Atrophicans Diffusa et Progressiva, *Arch Dermat & Syph* **33** 12-20 (Jan) 1936.

27 O'Leary, P. A., Montgomery, H., and Brunsting, L. A. Tuberculosis Cutis Indurativa (Idiopathic Atrophy? Poikiloderma?), *Arch Dermat & Syph* **35** 990-991 (May) 1937.

28 Oppenheim<sup>4</sup> Cannon, A. B., Karelitz-Karry, M. B., and Fisher, J. K. Poikiloderma-Like Change in the Skin Following Arsphenamine Dermatitis, *J. A. M. A* **118** 122-128 (Jan 10) 1942. Oppenheim, M., in discussion on Cannon, Karelitz-Karry and Fisher.

29 Hazel, O. G. Poikiloderma Atrophicans Vasculare. Report of a Case, *Arch Dermat & Syph* **40**: 776-791 (Nov) 1939.

25 Ormsby, O. S. Acrodermatitis Chronica Atrophicans, Generalized Lichen Planus or Poikiloderma? *Arch Dermat & Syph* **21** 666 (April) 1930. A Case for Diagnosis (Poikiloderma?), *ibid* **18** 304-305 (Aug) 1928. Acrodermatitis Chronica Atrophicans (Resembling Poikiloderma Vasculare Atrophicans), *ibid* **20** 388-389 (Sept) 1929.

recently, Benjamowitsch and Maschkilleisson<sup>30</sup> have given complete and thorough clinical distinctions between forms of scleroderma and acrodermatitis chronica atrophicans, which need not be repeated here. It is sufficient to reiterate that in none of the 45 cases in our series was there evidence of localized or generalized forms of scleroderma, acrosclerosis, Raynaud's disease, scleredema or dermatomyositis.

Distinction between acrodermatitis chronica atrophicans and erythrodermic forms of lymphoblastoma with or without poikiloderma-like changes may be difficult both clinically and histopathologically.<sup>31</sup> The infiltrate in acrodermatitis can be extensive and dense, simulating that seen in the lymphoblastomas. In both diseases there is frequently a considerable increase of histiocytes and reticulum cells.

We recently had under our care a man, an American teacher aged 49 years, who had had extensive diffuse generalized erythroderma and atrophy of the skin for twenty-two years associated with impetiginous and gummatous ulcers and whom we first regarded as presenting more extensive ulcers in acrodermatitis than those described by Oppenheim<sup>4</sup> and illustrated in the "Handbuch." There were extensive ulcerations involving the entire left leg, and subsequent biopsies revealed histopathologic changes strongly suggestive of a lymphosarcoma. The case histologically resembled somewhat a case previously reported by Goeckerman and one of us (H. M.)<sup>32</sup> It is possible that this patient had had acrodermatitis for twenty-two years and just recently a lymphoblastoma had become superimposed. This could be explained on the basis of malignant transition of the dense infiltrate of reticulum cells and histiocytes, but it seems more likely that the lesion has been a slow-growing progressive lymphoblastoma with erythrodermic and poikiloderma-like changes from the beginning.

As a rule, however, clinical or histopathologic distinction between lymphoblastoma and acrodermatitis chronica atrophicans is readily made on the basis of concomitant findings.

Various types of idiopathic macular atrophy, including anetoderma erythematodes of Jadassohn,

striae distensae and balloon lesions of the Schweninger-Buzzi multiple benign tumor-like new growths, have all been described in association with acrodermatitis chronica atrophicans.<sup>33</sup> Histopathologic studies were not made in the 1 case that we had of acrodermatitis chronica atrophicans associated with lesions of idiopathic macular atrophy. We had 2 patients with idiopathic macular atrophy without acrodermatitis chronica atrophicans in which the histopathologic changes, as has been described in the literature, were similar to those of acrodermatitis chronica atrophicans. It is our impression, however, from a review of the literature, especially the excellent studies by Chargin and Silver<sup>34</sup> and Scull and Nomland,<sup>35</sup> that although there is destruction of elastic fibers in both diseases there usually is much less infiltrate in idiopathic macular atrophy than in acrodermatitis and that the epidermis may be little affected, the rete ridges and papillary bodies remaining unaltered. This also applies to striae distensae and to the Schweninger-Buzzi balloon type of lesion.<sup>36</sup>

Macular atrophies also occur as secondary terminal manifestations to such diseases as syphilis, leprosy, lupus erythematosus and lichen planus and can be distinguished on the basis of concomitant findings.

#### MALIGNANT CHANGE

Epitheliomas (carcinomas) and sarcomas occasionally have been reported in association with acrodermatitis chronica atrophicans, but we believe that in many of these cases they were probably coincidental and not attributable to the disease and in others the diagnosis was not substantiated by histopathologic studies.

33 Hollander, L., and Schmitt, C. L. Atrophy of the Skin and Subcutaneous Fat, *Arch Dermat & Syph* **46** 414-418 (Sept.) 1942. Oppenheim<sup>4</sup> Sweitzer and Laymon.<sup>8</sup>

34 Chargin, L., and Silver, H. Macular Atrophy of the Skin, *Arch Dermat & Syph* **24** 614-643 (Oct.) 1931.

35 Scull, R. H., and Nomland, R. Secondary Macular Atrophy. A Study of Twelve Cases Occurring in Connection with Various Disorders, with Consideration of the Pathologic Relationships, *Arch Dermat & Syph* **36** 809-820 (Oct.) 1937.

36 In studies to be published by McNairy with one of us (H. M.), it appears that atrophic, balloon-like lesions associated with neurofibromatosis still show histologic evidence of neurofibromatosis and do not show simple atrophic changes in the elastic fibers, which would place the Schweninger-Buzzi condition in with the group of macular atrophies.

30 Benjamowitsch, E., and Maschkilleisson, L. N. Further Contribution to the Question Regarding Atrophy of the Skin. III. Acrodermatitis Chronica Atrophicans and Its Relation to Scleroderma, *Acta dermat* **14** 313-341, 1933.

31 Ebert, M. H., and Slepian, A. Lymphoblastoma, *Arch Dermat & Syph* **39** 581 (March) 1939.

32 Goeckerman, W. H., and Montgomery, H. Cutaneous Lymphoblastoma. Report of Two Unusual Cases, *Arch Dermat & Syph* **24** 383-395 (Sept.) 1931.

Slow-growing sarcomas have been reported in only 2 or 3 cases<sup>37</sup> If one accepts the concepts of Kyrle, Petges, Jessner and others that pseudosclerodermatous proliferation and fibrous nodules represent late attempts at repair in acrodermatitis chronica atrophicans, then one can conceive how this process could proceed further to malignant change

Most of the epitheliomas reported have arisen either from old stasis (varicose) ulcers or ulcers associated with pseudosclerodermatous infiltrations, especially those about the ankles There were 2 cases of the 45 in our series in which epitheliomas were found In 1 case a squamous cell epithelioma of grade 2 (Broders' method) developed from a stasis ulcer of the ankle which was of thirteen years' duration whereas acrodermatitis had been present only five years In the second case, a 75 year old woman had had senile keratoses of the face and recurrent epithelioma of the neck of many years' duration In addition, she had on the right flank a typical lesion of superficial epitheliomatosis, histologically basal cell in type which was of ten years' duration and which was situated in a pseudosclerodermatous band The acrodermatitis was generalized but of only two years' duration In neither of these 2 cases was any atrophy of the epidermis to be found adjacent to the epitheliomas, nor had the epitheliomas arisen from the atrophic skin The epitheliomas, therefore, in both of these cases can be presumed to represent a coincidental condition not related to the acrodermatitis In the third case of acrodermatitis chronica atrophicans, there was a large stasis ulcer of the ankle which had a pearly, rolled indurated border clinically strongly suggestive of a squamous cell epithelioma but which at the time of excision and graft proved histologically to be benign, with only a moderate degree of pseudoepitheliomatous hyperplasia

Pack and Wuester<sup>38</sup> in 1942 reported 4 cases of epithelioma in association with acrodermatitis chronica atrophicans and referred to the disease as a precancerous dermatosis, as did Slaughter<sup>39</sup>

more recently This perhaps may be attributable to MacKee and Cipollaro's<sup>40</sup> inclusion of acrodermatitis chronica atrophicans with precancerous dermatoses, using this term in the broadest sense and not, as one of us (H M) had done, limiting the term to a few dermatoses in which epithelioma happens to develop in 20 per cent or more of the cases and which are characterized histologically by squamous cell epithelioma in situ<sup>41</sup> Pack and Wuester stated that most basal and squamous cell epitheliomas are scar cancers We cannot agree with this view They failed to distinguish between hypertrophic and atrophic scars Thus, as Counseller, Craig and Montgomery<sup>42</sup> have shown, epitheliomas frequently arise from leukoplakia but not, as a rule, from kraurosis vulvae unless leukoplakia has first supervened Senile, roentgen ray, radium, arsenic and tar keratoses are true precancerous lesions Epitheliomas arising from chronic ulcers of the leg due to burns, varices and so forth occur in less than 6 per cent of the cases and are not true precancerous lesions

On further analysis of Pack and Wuester's 4 cases, one finds that in their first case of acrodermatitis chronica atrophicans with epithelioma the disease was limited to the axillary regions and upper part of the arms, a distribution of lesions which does not correspond to that in any case previously reported, that the patient had had eighteen roentgen treatments, including the treatment of palpable lymph nodes, and that histologically the epithelioma was of the type one would associate with radiodermatitis Illustrations of the second case show senile keratoses on the backs of the hands, suggesting origin of the epithelioma of the hand on this basis No statement is made as to the origin of the ulcers on the ankles, although there is no question that the patient also had acrodermatitis chronica atrophicans In their third case, one might be justified in presuming that the epithelioma arose from senile keratosis rather than from the atrophic skin In their fourth case, despite the history of "great varicosities" of both legs, the

37 Seifert, H-H Multiple maligne Tumoren auf den Boden einer Acrodermatitis atrophicans chronica Dermat Wchnschr 99:1234-1240 (Sept 22) 1934  
Klaar I Ein Fall von Acrodermatitis chronica atrophicans mit Sarkombildung Arch f Dermat u Syph 134 160-170 1921

38 Pack, G T, and Wuester, W O The Development of Cancer in Acrodermatitis Chronica Atrophicans I A M A 118 879-884 (March 14) 1942

39 Slaughter, D P The Role of Surgery in the Treatment of Malignant Skin Tumors, Surgery 14 732-746 (Nov) 1943

40 MacKee, G M, and Cipollaro, A C The Treatment of Precancerous Lesions of the Skin, in Pack, G T, and Livingston, E M The Treatment of Cancer and Allied Diseases, New York, Paul B Hoeber, Inc, 1940, vol 3, pp 1999-2026

41 Montgomery, H Precancerous Dermatoses and Epithelioma in Situ, Arch Dermat & Syph 39 387-408 (March) 1939

42 Montgomery, H, Counseller, V S, and Craig, W M Kraurosis, Leukoplakia and Pruritus Vulvae Correlation of Clinical and Pathologic Observations with Further Studies Regarding Resection of the Sensory Nerves of the Perineum, Arch Dermat & Syph 30:80-100 (July) 1934



lesion must presumably be accepted as a squamous cell epithelioma developing in atrophic skin of acrodermatitis chronica atrophicans, although no histologic details were given regarding the presence of varices or changes in the epidermis adjacent to the epithelioma. Wise<sup>43</sup> gave a brief report of a case of acrodermatitis chronica atrophicans in which squamous cell epithelioma developed as an ulcer in the atrophic skin on the inner aspect of the right thigh and remained healed after treatment. No details are given as to the method of treatment or whether the diagnosis was confirmed by histologic examination.

The few other cases of epithelioma on acrodermatitis chronica atrophicans reported in the literature are difficult to evaluate because of the lack of sufficient data. If one excludes epitheliomas that arose from stasis ulcers or from senile keratosis, then the incidence of epitheliomas in acrodermatitis chronica atrophicans at most is only a few per cent.

We object to the designation of acrodermatitis chronica atrophicans as a precancerous dermatosis because if one so designates this disease then a great many common dermatoses, such as psoriasis and lichen planus, in which epitheliomas rarely are seen independent of any treatment would also have to be included under this term.

#### TREATMENT

There is no known treatment for acrodermatitis chronica atrophicans that is satisfactory, although all types of treatment from endocrine therapy to the use of vitamins have been employed and in solitary cases patients have been reported as being benefited by one or more methods of treatment. All the patients in our series of cases received multiple types of therapy without any appreciable benefit.

We were pleasantly surprised to find that in several cases in which pseudosclerodermatous or stasis ulcers about the ankles were excised and grafted the grafts, on the whole, took well. The same was true in regard to the 2 cases in which there was epithelioma and in which healing took place after excision with or without grafting.

#### SUMMARY AND CONCLUSIONS

Acrodermatitis chronica atrophicans is a chronic dermatosis of unknown cause usually involving the extremities, especially the extensor surfaces in the vicinity of the knees, ankles, el-

bows and wrists. The disease, however, may be generalized and appear as erythroderma with poikiloderma-like changes. At times it may be unilateral. It is not limited to one nationality or continent, and it occurs fairly frequently among native-born Americans. It is usually a disease of the later decades of life, predominating in women who are more than 40 years of age. Pseudosclerodermatous changes, with considerable scaling and thickening of the skin about the ankles, with or without ulcers occur in about a third of the cases. So-called ulnar bands, fibrotic nodules and stasis ulcers are less frequent than pseudosclerodermatous changes. The histopathologic changes are distinctive if a specimen for biopsy is taken from a well developed area of atrophy. There is preservation of a border zone of connective tissue between the flattened epidermis and the infiltrate in the cutis, but there is much destruction of connective and elastic tissue where the infiltrate occurs, resulting in pronounced thinning of the cutis. This destruction of collagenous and also elastic tissue might be caused by unknown toxic substances associated with the infiltrate. Acrodermatitis chronica atrophicans, especially in its generalized erythrodermic forms, can be distinguished from other atrophic dermatoses on the basis of concomitant clinical and histopathologic changes. Acrodermatitis chronica atrophicans is not a precancerous dermatosis. There is no adequate form of therapy known. The disease usually runs a benign course and does not reveal definite association with any systemic disease that may coincidentally be present, especially among the more elderly patients.

#### ABSTRACT OF DISCUSSION

DR. FRED WISE, New York. This contribution is a comprehensive review of the subject of acrodermatitis chronica atrophicans and adds chiefly to the knowledge of its histopathology. The authors stress the point that the histologic structure of a well developed area of atrophy is distinctive, enabling one to make a diagnosis microscopically. The average histopathologist has much difficulty in differentiating the end stage of this disease from the end stages of other cutaneous atrophies. But one must bear in mind that the authors' findings are based on biopsies from 20 patients, which is probably an all time record for this disease.

Concerning the clinical aspects, little can be added to the descriptions in Finger and Oppenheim's monograph, published in 1910 (Finger, E., and Oppenheim, M. *Die Hautatrophien*, Vienna and Berlin, F. Deuticke, 1919). Most patients consult the dermatologist when the disease is in an advanced stage and the diagnosis may be made almost at a glance. Occasionally one encounters early changes, for example, a faint, pink band, extending from the base of the fingers on the dorsal aspect of one hand to the region of the elbow, this band is not infiltrated, may have well defined borders and its surface is smooth and glistening, the veins appearing

<sup>43</sup> Wise, F. Acrodermatitis Chronica Atrophicans with Healed Squamous Cell Epithelioma, *Arch Dermat & Syph* 15 230-231 (Feb.) 1927.

to be a little more conspicuous than those on the unaffected hand. Careful examination is demanded in such cases, especially with respect to early changes in the skin of the lower extremities. The patients are requested to report for further examination at six month intervals. Judging from my experience, concomitant cutaneous and visceral lesions are rare. One patient with sarcoma of the ankle and 1 with epithelioma of the thigh have come under observation.

The authors mention chronic arthritis as a complication of the disease, referring to the case described by Sweitzer and Laymon in 1935. Their patient had a peculiar deformity of the hand, having the appearance of a hand that had been forcibly flexed and twisted outward. The diagnosis of atrophic arthritis with deformity was confirmed by roentgen examination. Within the past three years, two similar instances were observed at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. Both patients were men who also had extensive areas of diffuse idiopathic atrophy of the extremities and trunk,

but the eruption as a whole did not resemble acrodermatitis chronica atrophicans but appeared rather to be an atrophy following a long-standing diffuse erythroderma. I am inclined to the belief that such arthritic changes, as well as associated cutaneous malignant growths, are not intrinsic complications of acrodermatitis chronica atrophicans.

I have had no successful results from therapy. At the present time 1 of my patients is taking dihydro-tachysterol but it is too soon to determine its effect on the skin.

DR HAMILTON MONTGOMERY, Rochester, Minn. I am glad to have Dr. Wise mention the reported roentgenologic changes in the bones and arthritic changes, and I am in accord with him that they are coincidental rather than a fundamental part of the picture.

Dr. Wise probably has seen more cases of acrodermatitis chronica atrophicans than any one else in the United States, and I am therefore deeply appreciative of his discussion of this paper.

## Clinical Notes

### HYPERSENSITIVITY TO EPHEDRINE

#### Report of a Case

GERALD A. SIENCLER, M.D., NEW YORK

Because of the extensive use of ephedrine as one of the principal active ingredients in many nose drops, I wish to present this case, in which there was an acute eczematous eruption occurring around the nostrils and a possible dermatitis medicamentosa on other portions of the body. Both eruptions seemed to be caused by an oily inhalant which contained ephedrine.

#### REPORT OF CASE

R. J., a 34 year old Negro woman, was seen by me because of an acute eruption on her face and body. She stated that two days prior to the appearance of the eruption she had used an oily preparation as nose drops to abort an acute rhinitis. The eruption, which first began around the nostrils, spread to the forehead and finally to other parts of her body.

Examination showed an acute erythematous papulo-vesicular and scaling eruption around the nostrils and on the upper lip, which extended about 2 inches (5 cm) to both sides of the nose (fig 1). On the forehead, there were several discrete erythematous and papular lesions which extended down to the neck. On the upper and lower limbs and on the trunk similar papular lesions were observed (fig 2). The upper part of the

nasal tract and pharynx were extremely red and edematous. The rest of the examination revealed nothing relevant.

A patch test was made on the inner aspect of the arm with the oily inhalant. It elicited a positive reaction. The contents of the preparation as presented on the label were as follows, camphor, menthol, eucalyptol and ephedrine. Patch tests were then performed with 1 per cent menthol, 1 per cent eucalyptol, 1 per cent camphor and 1 per cent ephedrine each dissolved in liquid petrolatum. All elicited negative reactions with the exception of the ephedrine which elicited a positive reaction.

It was not possible to obtain information as to any previous sensitivity to the drug.

#### COMMENT

The eczematous eruption around the nasal orifices was apparently the result of direct contact with and local sensitivity to ephedrine, whereas the eruption on the face, neck and other portions of the body might be considered as a hematogenous spread, either through local absorption or by ingestion of the drug.

2135 Seventh Avenue



Fig 1—Eczematous eruption around the nostrils and on the upper lip and discrete papular lesions on the forehead and neck

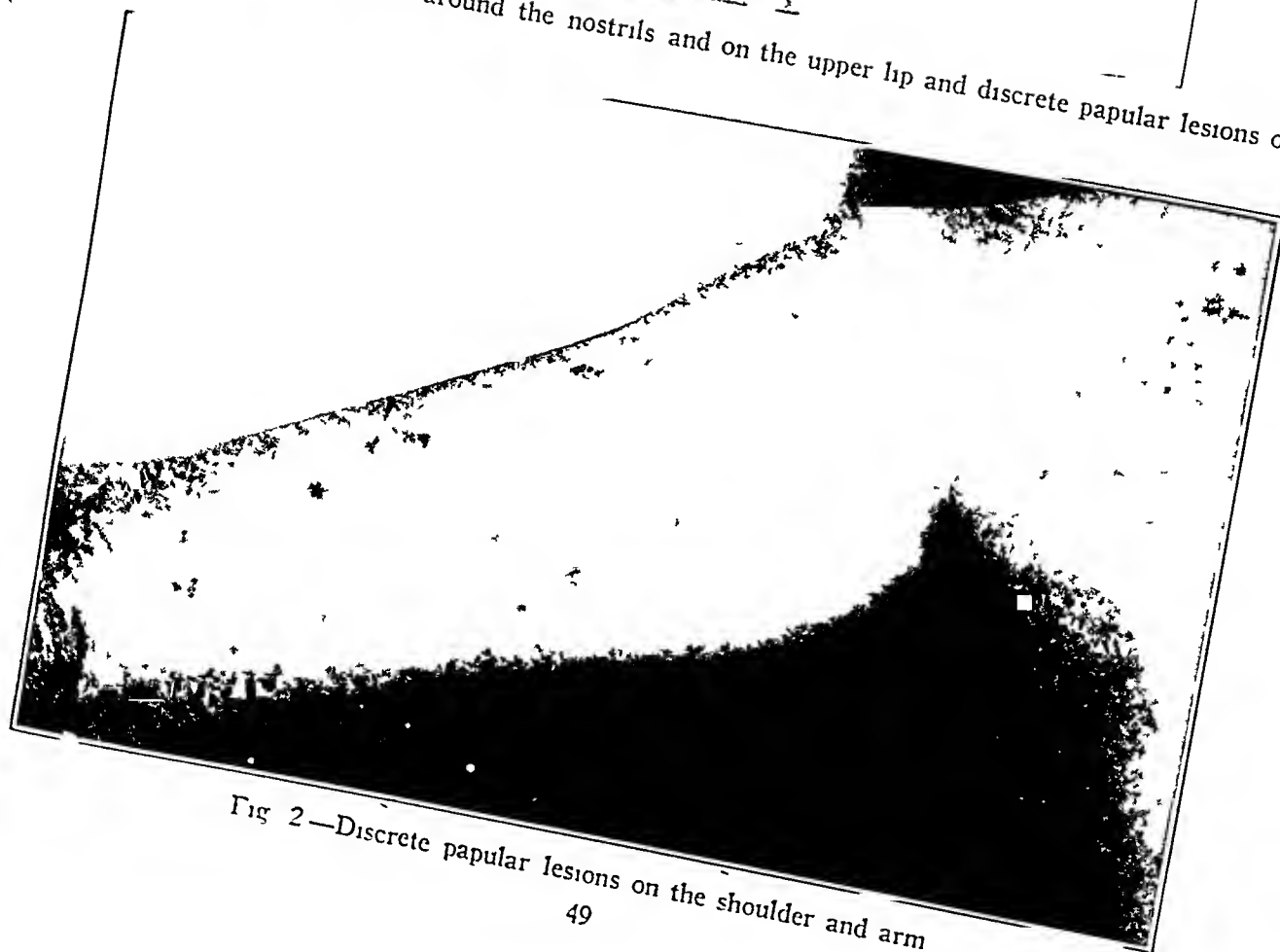


Fig 2—Discrete papular lesions on the shoulder and arm

# Abstracts from Current Literature

EDITED BY DR HERBERT RATTNER

RELATIONSHIP OF LYMPHOGRANULOMA VENEREUM INFECTION TO THE INCIDENCE OF HYPERGLOBULINEMIA  
PAUL B. BEESON and EDWARD S. MILLER, *Am J M Sc* **207** 643 (May) 1944

Because of the prevalence of lymphogranuloma venereum in the Negro population in Georgia, a study was made of the incidence of hyperglobulinemia in 2,375 serums from both the white and the Negro population. The "formol-gel test" (jelling of the serum in the presence of solution of formaldehyde) was used to detect the presence of increased globulin. Hyperglobulinemia was more than ten times as frequent in the serums of Negroes as in the serums of white persons and was found in a slightly higher proportion of women than of men, 56 per cent of Negro men and 83 per cent of Negro women. Increased globulin was more frequent in the serums of persons with syphilis, but it is thought not to be caused by the syphilis but rather to result from the fact that persons who have acquired one venereal disease are apt to have acquired another. There were 13 instances of hyperglobulinemia among 125 serums with positive Kahn reactions. Seventy-four gave a positive reaction for lymphogranuloma venereum, and this group included 12 of the serums showing hyperglobulinemia. This appears to be a significant difference and points to lymphogranuloma venereum rather than to syphilis as the principal cause of hyperglobulinemia.

TUMEFACATION OF SUBCUTANEOUS FAT FOLLOWING THE INJECTION OF INSULIN. A CLINICAL AND HISTOLOGIC STUDY. HUGO T. ENGELHARDT and VINCENT J. DERBES, *Am J M Sc* **207** 776 (June) 1944

A case of localized fat tumefaction following administration of insulin is presented, and the authors point out the paradoxical effects of injection of insulin on subcutaneous fat, on the one hand, atrophy may follow and, on the other, fatty tumefaction may result. All writers on the subject appear to be in agreement that lipoid tumefaction following administration of insulin appears chiefly in children.

LYNCH, St Paul

A SEVERE REACTION FOLLOWING ADMINISTRATION OF DIASONE. KARL H. PFUETZE and MARJORIE M. PYLA, *J A M A* **125** 354 (June 3) 1944

After the administration of diasone (the disodium formaldehyde sulfoxylate derivative of diaminodiphenyl-sulfone) for three weeks to a tuberculous patient, a pemphigus-like eruption appeared. This was followed by an exfoliative dermatitis. The patient's palate and pharynx were covered by a red punctate rash.

CONTACT DERMATITIS FROM PENICILLIN. H. D. PYLE and HERBERT RATTNER, *J A M A* **125** 903 (July 29) 1944

Pyle and Rattner report a case of contact dermatitis from penicillin in a medical officer in charge of preparing the various solutions as well as of administering the drug to patients. The eruption began as a mild marginal blepharitis and conjunctivitis. It soon spread

to the bridge of the nose, the forehead and the central oval of the face. It had the characteristics of a relatively acute dermatitis due to contact with an irritant. In the course of a few weeks eczematous lesions appeared on the hands and penis. When the patient was relieved of handling penicillin, the eruption completely disappeared in a fortnight. When he was again exposed to penicillin, the eruption recurred. A patch test with penicillin elicited a strongly positive reaction. Additional patch tests indicated that it was the penicillin and not the medium on which it is cultivated which was responsible for this contact dermatitis.

HEINSCHIR, Denver

THE ADMINISTRATION OF NICOTINIC ACID AND CALCIUM LACTATE IN URTICARIA. DORRIS COSS CHAMBERS and HARRY S. BERTON, *J Allergy* **15** 141 (March) 1944

Chambers and Berton administered 20 mg of nicotinic acid twice daily and 5 grains (0.3 Gm.) of calcium lactate three times daily to 15 patients suffering from urticaria. The results were gratifying, great improvement was produced within twenty-four to forty-eight hours, and complete clearing of the skin resulted in three or four days. After the attacks subsided, the authors found that the nicotinic acid could be reduced to 20 mg per day for about ten days and then given every other day, with discontinuance after one month. The nicotinic acid was given with meals to avoid the flushing and tingling of the skin that sometimes follows if it is taken in the postoperative state.

In 2 patients a coexisting asthma was likewise benefited by this therapy.

VITAMIN B<sub>1</sub> HYPERSENSITIVITY WITH DESENSITIZATION. REPORT OF A CASE. MOISES M. MITRANI, *J Allergy* **15** 150 (March) 1944

The author reports a case of a macular pruriginous eruption in a 15 year old girl, involving the face, chest and back. The eruption appeared after the first injection of 50 mg of a commercial preparation of thiamine hydrochloride and chlorobutanol, in a saline solution. Subsequently three similar daily injections produced the similar results.

Intradermal tests to five different brands of thiamine hydrochloride gave 3 plus reactions, the saline solution and the chlorobutanol elicited negative reactions. A Prausnitz and Kustner passive transfer test elicited positive reactions to the five brands of thiamine hydrochloride.

Desensitization was accomplished by daily subcutaneous injections of solution of thiamine hydrochloride in small increasing doses until the patient tolerated a dose of 1 cc containing 100 mg.

Evidence of desensitization was based on cessation of symptoms with continued use of thiamine hydrochloride and a negative reaction to an intradermal test with this drug.

MENDELSON, New York

USE OF DRIED RED BLOOD CELLS IN WOUND HEALING  
T H SELDON and H H YOUNG, Proc Staff Meet,  
Mayo Clin 18 385 (Oct 20) 1943

Infected wounds, postoperative abdominal wounds which had not healed above the fascial layer, certain proctologic wounds, varicose and other ulcers of the leg, amputation stumps and open chest wounds were treated with the dried powdered red blood cells. The results were not uniformly beneficial but were sufficiently promising to warrant more investigative work.

GIOMUS TUMORS DIAGNOSIS AND TREATMENT J  
G LOVE, Proc Staff Meet, Mayo Clin 19 113  
(March 8) 1944

Probably 50 per cent of glomus tumors, or at least the symptoms of the tumors, appear after some trauma which may be relatively trivial. The symptoms are out of proportion to the size of the lesion. The tumor is usually not more than a few millimeters in diameter. It is most commonly seen on the extremities, under the nail. Usually the patient complains of severe paroxysms of pain which seem to originate at the site of the lesion. The lesions are sometimes extremely small, and therefore if the typical purplish color is absent they may not be seen. The question of whether or not these lesions may become malignant is debatable. Generally glomus tumors are considered benign.

Love has found the test which he elects to call the "pin" test valuable in the diagnosis and localization of this tumor. A steel pin is used to examine around the lesion. The point of the pin can be pressed into the skin as near as 1 cm to the lesion without producing severe pain, but just as soon as the point is pressed over the lesion the patient will have an excruciating attack of the characteristic pain projecting from the lesion. On many occasions when the author was unable to see the lesion, he was able to identify its location and make the diagnosis with the help of the pin.

The treatment of tumors is surgical excision. Immediate relief of pain does not occur after complete removal of the lesion.

PENICILLIN IN THE TREATMENT OF EXPERIMENTAL INFECTIONS DUE TO ERYSIPELOTHRIX RHUSIOPATHIAE F R HEILMAN and W E HERRELL, Proc Staff Meet, Mayo Clin 19 340 (June 28) 1944

Erysipeloid is an infection caused by the organism of swine erysipelas, *Erysipelothrix rhusiopathiae*. The only available treatment has been the use of immune serum. Sulfonamide compounds are ineffective in the treatment of the clinical disease as well as of the experimentally produced disease in mice. Heilman and Herrell have studied the in vitro and in vivo effects of penicillin on the causative organism. In vitro tests indicate that *Ery rhusiopathiae* is sensitive to the action of penicillin. For the in vivo studies, 40 mice were inoculated with a virulent culture of *Ery rhusiopathiae* and 40 mice were untreated. All of the untreated mice died. Of the 40 mice treated with penicillin, only 2 died.

THE PATCH TEST IN CONTACT DERMATITIS LOUIS  
SCHWARTZ and SAMUEL M PECK, Pub Health Rep  
59 1 (April 28) 1944

A complete resume of the authors experience with patch test in the diagnosis of contact dermatitis is

given. The technic of the patch test, variations in technic and especially modifications of the patch test for particular problems are discussed in detail. The complications and medicolegal aspects of patch testing are discussed as well as the use of the patch test to prevent outbreaks of dermatitis from the introduction of new chemicals, etc. The authors have termed this procedure the "prophetic patch test".

THE CHEMOTHERAPY OF BURNS AND SHOCK VI  
STANDARDIZED HEMORRHAGE IN THE MOUSE VII  
THERAPY OF EXPERIMENTAL HEMORRHAGE HERBERT TABOR, HERMAN KABAT and SANFORD M ROSENTHAL, Pub Health Rep 59 637 (May 19) 1944

The authors describe a method whereby a large number of unanesthetized small laboratory animals can be subjected simultaneously to standardized hemorrhage. The results obtained in this paper along with those previously published on burn and traumatic shock indicate that administration of specific electrolytes and fluid is of greater significance in therapy than administration of plasma proteins.

Whole blood is superior to isotonic solution of sodium chloride or serum. The response to whole blood given intravenously can be equaled by three times the volume of saline solution given orally. Erythrocytes suspended in isotonic solution of sodium chloride are as effective as equal volumes of whole blood. These facts indicate the importance of red cells in the therapy of hemorrhage. The experimental evidence would seem to justify the clinical trial of sodium salts administered in isotonic solution in part or entirely by mouth in amounts up to 10 per cent of body weight in the treatment of burn shock, traumatic shock and hemorrhage. For war casualties, particularly where intravenous medication is not immediately available, the procedure may be of value as a first aid measure.

SULFARSPHENAMINE IN THE THERAPY OF SYPHILIS A  
COMPARATIVE STUDY OF THE TOXIC MANIFESTATIONS OF NEOARSPHENAMINE AND SULFARSPHENAMINE THOMAS F PROBEY, EDGAR W NORRIS, AUSTIN V DEIBERT and ELEANOR V PRICE, Pub Health Rep 59 733 (June 9) 1944

This study presents a clinical comparison of the reactivity of neoarsphenamine and sulfarsphenamine in the treatment of syphilis. The reaction rate for neoarsphenamine is only slightly less than that for sulfarsphenamine, although the total rates are approximately the same. Sulfarsphenamine appears to be a particularly toxic drug for white women.

Of the minor reactions, gastrointestinal (268 per thousand) and febrile (60 per thousand) occurred most often after neoarsphenamine therapy, in the group receiving sulfarsphenamine gastrointestinal reactions (266), slight eruptions (76) and pruritus (57) were most frequently encountered. With neoarsphenamine therapy, icterus (33) and dermatitis (26) were the major reactions of importance, with sulfarsphenamine, dermatitis (31) and purpura hemorrhagica (29). The significant observation of the comparative study of reactivity of neoarsphenamine and sulfarsphenamine is that icterus occurred most frequently after neoarsphenamine, and purpura most frequently after sulfarsphenamine. Concurrent treatment with sulfonamide compounds and neoarsphenamine had no influence on the reaction rates, but when sulfonamide compounds were combined

with sulfaisphenamine the incidence of purpura hemorrhagica (61) was two and one-half times as frequent as when sulfaisphenamine (24) was administered alone.

Sulfaisphenamine is less toxic in patients receiving the first course of therapy than is neoarsphenamine, but, conversely, neoarsphenamine is less toxic than sulfarsphenamine in patients receiving the second and especially the third course of therapy.

PICK, Bethesda, Md

THE ROLE OF THE SULFONAMIDES IN DERMATOLOGY  
REGINALD S. HEATHCOTE, Brit J Dermat 56 59  
(March-April) 1944

The sulfonamide compounds affect chiefly or exclusively the metabolic processes of the organism, and as the drugs are more effective in febrile than in afebrile patients metabolism will proceed more rapidly at the higher temperature. This may explain why sulfonamide compounds are more efficient against infections with virulent than against infections with avirulent organisms. In the treatment of gonorrhea, a disease not associated with fever, better results have been claimed for the drugs in cases in which they were used simultaneously with hyperthermia.

The risk of inducing resistance in the infecting strain must always be borne in mind. The process takes a little time to develop, and the organisms may by then be so reduced in number that the ordinary defensive processes of the body can deal with them satisfactorily, for the resistant bacteria are just as susceptible as the nonresistant to the effects of antiserums. Nevertheless it is desirable to adopt the tactics of the *Blitzkrieg* by beginning with large doses, so as to obtain quickly a relatively high blood concentration of the drug and to continue such doses as will maintain that level as nearly constant as possible.

SULFONAMIDES IN DERMATOLOGY DONALD M. PILLSBURY, Brit J Dermat 56 68 (March-April) 1944

Various sulfonamide compounds are effective in the treatment of superficial pyogenic infections of the skin, particularly impetigo. Sulfathiazole in 5 per cent strength is more effective than sulfadiazine, sulfanilamide or sulfapyridine. The type of base used is important, and water in oil or oil in water emulsions appear to be definitely superior to others.

The technic of treatment is also important. Substances which inhibit the action of sulfonamide compounds, such as crusts and pus, must be removed by mechanical cleansing at least once a day.

It appears that in persons with chronic dermatoses in which there is an element of sensitivity, particularly to pyogenic bacteria or their products, sensitivity to sulfonamide drugs, especially sulfathiazole, may easily be induced by topical application. This case of sensitization offers a serious contraindication to topical use of sulfonamide compounds for such diseases.

In the treatment of acute superficial pyoderms, when the period of application was not longer than five days sensitization reactions to sulfonamide drugs have not been encountered in frequency or in severity sufficient to militate against the over-all usefulness of this type of therapy. Nevertheless, the justifications for such therapy must still be regarded as sub judice. The need for effective sulfonamide compounds with lower sensitizing properties than those now available is apparent.

SEBORRHOIC SKIN ERUPTIONS J. A. SCOTT, Brit J Dermat 56 80 (March-April) 1944

In the author's opinion the seborrheic state or diathesis, results primarily from an excessive consumption of carbohydrate foods and fats and an excessive intake of fluids. This leads to a retention of fluids in the tissues if the kidneys are not unduly permeable to water. The contributory factors are an endocrine imbalance (not yet fully studied), which affects chiefly persons at the ages of puberty and the climacteric (male and female), and a deficiency in the intake or the absorption of vitamin C.

The tissues or organs affected and the type and site of the lesions depend on the presence of a congenital or an acquired weakness (locus minoris resistentiae), prolonged but mild exposure to external irritants such as sun wind, dust, occupational irritants and cosmetics, the presence of circulating toxins or poisons such as alcohol, bacterial toxins and food toxins, and the presence of bacterial infections, scabies, pediculosis and various infestations.

In an obese person symptoms and signs are delayed as long as fat is freely produced from the digestion and the absorption of fatty foods and from dextrose, which is formed in excess. The fat fixes the toxins and other poisons which have escaped normal destruction. When fat is no longer produced in sufficient amount or is saturated by these toxins and poisons, the signs and symptoms of the diathesis appear, and true diabetes mellitus (pancreatic exhaustion or disease) is also encountered. Bacterial infections have then a free and suitable field of action. This explains why obese persons remain in excellent health for so long and why their resistance to bacterial infections breaks down suddenly.

The author is of the opinion that the renal excretion of water, which varies enormously in different persons, has an important bearing on the signs and symptoms of the seborrheic diathesis. When excretion of water is rapid, there is no time for it to invade the skin and other organs and tissues and the diathesis is nonexistent or at least symptomless. Excessive drinking of fluid in such a case leads to debility from excessive loss of sodium chloride and other mineral salts.

BLUEFARB, Chicago

KOILONYCHIA AND POLYCYTHAEMIA VERA A. J. GLAZEBROOKE, Edinburgh M J 51 65 (Feb) 1944

Koilonychia (spoonlike concavity of the nails) developed in association with other symptoms in a patient with polycythemia vera described by Glazebrooke. General roentgen irradiation reduced the red blood cell count and greatly increased the serum iron value, and healing of the koilonychia occurred. Koilonychia has frequently been reported in association with microcytic and hypochromic anemias. This case and other evidence suggest that the changes in the nails result from iron deficiency rather than from the anemia (though that, too, may be due to iron deficiency).

LANCH, St Paul

THE INCIDENCE OF TETRYL DERMATITIS OR "CE" RASH H. M. L. MURRAY, R. W. PRUNSTER and R. D. ANDERSON, M J Australia 1 104 (Feb 5) 1944

The major manifestation of exposure to tetryl is "CE" rash. Typically this rash resembles fairly acute



follicular dermatitis. It normally affects those portions of the face which are best supplied with sebaceous glands. The follicular stage is usually followed by some swelling, vesiculation and crusting. The rash is associated almost entirely with tasks which require actual handling of the explosive. For new employees, the major risk of rash occurs between the fourteenth and twenty-fourth days of employment. The seasonal incidence is at a maximum between August and October and at a minimum in January and February.

A RECORD OF COMMONER SKIN DISEASES AT A ROYAL AUSTRALIAN AIR FORCE HOSPITAL. BEN O'COLAHAN, M. J. Australia 1 107 (Feb 5) 1944

During the year 1942 over 500 patients with dermatologic diseases were treated at a Royal Australian Air Force hospital. The five cutaneous diseases most frequently seen were impetiginous infections of the face and neck, axillary hyperhidrosis and intertrigo, seborrheic dermatitis and seborrheic intertrigo, dyshidrotic conditions of the feet and pyogenic infections of the legs.

HANSCHER, Denver

## Correspondence

### VITAMIN A DEFICIENCY OF THE SKIN

To the Editor.—I read with interest the article on "Clinical Manifestations of Vitamin Deficiencies as Observed in the Federated Malay States" by Dr. Paul Fasal (ARCH DERMAT & SYPH 50 160 [Sept] 1944).

The clinical features and histopathologic changes correspond with those described in my report of an investigation in China (Reiss F. A Contribution to Cutaneous Manifestations of Vitamin-A Deficiency, Chinese M J 50 945 [July] 1936). In addition to the perleche-like lesions described, I also noticed, not infrequently, transverse furrows of the nail plates. In contrast to the lesions of Dr. Fasal's patients, the perleche-like lesions of all our patients disappeared under cod liver oil therapy simultaneously with the disappearance of the cutaneous manifestations. It appears to me, therefore, that the cutaneous manifestations are an indication of a deficiency or a lack of vitamin-A primarily rather than of a deficiency of the vitamin B factor.

While I admit that perleche-like lesions have frequently been observed in China in persons with riboflavin deficiency, the cutaneous lesions, however, had nothing in common with the cutaneous follicular manifestations observed in association with vitamin A deficiency. I feel that prolonged and well controlled cod liver oil medication takes care of the perleche-like

lesions and that the introduction of riboflavin or the vitamin B complex in the therapy of the well established disease syndrome weakens rather than confirms the concept of vitamin A deficiency of the skin.

FREDERICK REISS, M.D., New York

### NOTICE

The Scientific Session of the 1945 meeting of the Section on Dermatology and Syphilology of the Medical Society of the State of New York will be held at the Hotel Statler in Buffalo on Wednesday and Thursday mornings, May 2 and 3, 1945.

Members of the Medical Society of the State of New York who wish to present papers will please forward their titles to the Secretary before Feb. 1, 1945.

E. WILLIAM ABRAMOWITZ, M.D., Secretary

853 Seventh Avenue, New York 19

### CORRECTION

The title of the article by Dr. Hal E. Freeman which appears in the November issue (ARCH DERMAT & SYPH 50 320, 1944) should read "Aplastic Anemia with Thrombopenic Purpura and Agranulocytosis Complicating Mapharsen Therapy."

# Society Transactions

## MANHATTAN DERMATOLOGIC SOCIETY

ANTHONY C. CIPOLLARO, M.D., *President*

WILBERT SACHS, M.D., *Secretary*

*Dec 14, 1943*

### A Case for Diagnosis (Solid Edema? Milroy's Disease?) Presented by DR. E. WILLIAM ABRAMOWITZ

M. A. E., a white man aged 58, appeared at my office on Sept. 24, 1943. According to his past history, an eruption developed on his right palm in 1916. He received treatment at the New York Skin and Cancer Hospital and showed slight improvement. Five or six years later (about 1922) the eruption spread to his left palm. At that time he also had some trouble with the joints of his finger for which he received treatment at the Hospital for Joint Diseases. In 1926 he was given roentgen ray treatment at the Polyclinic Hospital for "eczema" on his hands.

In 1935, suddenly and for no apparent reason, there developed swelling on the backs of his hands accompanied by redness. Recurrent attacks of swelling and redness have appeared several times weekly up to the present time. There have been no constitutional symptoms with these attacks.

The backs of his hands are now edematous and show moderate redness. When he has a relapse, the redness and swelling become more pronounced. The patient states that he has no knowledge of a similar condition of the hands, legs or other parts of the body in his parents or siblings. Recently, after a pinprick, an infection developed which was followed by erythema and scaling of the palms, for which he received compensation. With roentgen ray therapy his hands have shown some improvement.

#### DISCUSSION

DR. DAVID BLOOM: I believe that the edema in this case is due to the chronic eczema of the hands from which the patient has been suffering for many years. The redness of the skin and the age at which the edema developed are also points against the diagnosis of Milroy's disease.

DR. MAURICE J. COSTELLO: I think that the patient has solid edema, and if one of the sulfonamide compounds has not already been tried I think it would be well worth while to do so. I have greatly improved, if not cured, patients with solid edema of years' standing with moderate doses of sulfanilamide or sulfathiazole over a fairly long period. I can recall 3 patients who were definitely improved, and 1, I think, was cured. Sulfanilamide was used in the last-mentioned case.

DR. GEORGE C. ANDREWS: I cannot but be impressed with the carious and bad condition of the teeth. The patient has old abscessed roots and severe pyorrhea. Dental roentgenograms were made, and it was advised that all teeth should be extracted. It is hard to prove satisfactorily that there is any connection with the edema of the hands, but I certainly should not want to give the edema of the hands a classic name and be

satisfied without doing something else. I think the patient should be put in good general health, having the teeth fixed first.

DR. GEORGE M. LEWIS: The point raised by Dr. Andrews seems important. The man deserves eradication of all foci of infection, and, since no better cause has been brought forward, I should await developments until that has been done.

DR. ISADORE ROSEN: I agree with those who believe that the disease is due primarily to a chronic recurrent inflammatory condition of both hands. From the history, the patient has had a recurring chronic eczematous dermatitis. As a result of this, there was a certain amount of damage done to the lymph vessels, producing a lymph stasis. Similar changes occur on the lower extremities following the erysipelas-like manifestations associated with chronic dermatophytosis.

DR. E. WILLIAM ABRAMOWITZ: This man was a violinist and had to give up his profession because of the swelling of the hands. He has bad teeth and is being treated at a dental clinic. Since receiving roentgen treatment to the hands, he has not had an attack, whereas he formerly had two or three attacks a week. The location is unusual, but it may occur in this area, depending perhaps on a neighboring focus of infection. The use of sulfonamide compounds was suggested some time ago, and it is frequently of help for patients who have recurrent attacks of fever and erysipelous lesions of the skin. Elephantiasis of the legs is helped by Kondoleon's operation. Unfortunately, the patients are subject to recurrences, with resultant enlargement. Patients with Milroy's disease are also subject to these febrile and erysipelous attacks.

### Solid Edema of the Face Presented by DR. JACK WOLF

A. J., a man aged 52, first consulted me on July 23, 1943, complaining of swelling of the face. He stated that this swelling had appeared suddenly about three years previously and had persisted in spite of numerous forms of treatment, including the administration of sulfanilamide and roentgen therapy.

The right lower eyelid is pronouncedly edematous, and the fullness stands out in contrast to the normal appearance of the left lower lid. The portion of the cheek beneath the lid is also enlarged and stands out prominently. There is no change in color. On palpation, the affected part of the cheek is of a rubbery consistency and lacks the suppleness of the normal skin.

Examinations by several ophthalmologists and otolaryngologists did not reveal any abnormality which would account for the swelling.

The patient obtains a measure of relief by wearing a specially made pressure bandage at night, which apparently reduces the edema for a number of hours during the day.

#### DISCUSSION

DR. MAURICE J. COSTELLO: Has this patient received vaccines? They would be worthy of trial.

DR. GEORGE C. ANDREWS: I should give this man some injections of a sterile milk preparation as non-specific protein therapy. I am not convinced that it

solid edema. In the cases I have seen the lesions were distinctly circumscribed. Whereas the lesion on the right lower lid might be so considered, there is in addition to edema a redness of the skin over both lesions which looks like dermatitis venenata. The lesion on the left side of the forehead is not circumscribed but is rather a diffusely erythematous and edematous patch, with poorly defined edges.

DR GEORGE M. LEWIS: Because of the presence of numerous minute vesicles, I thought of dermatitis venenata as the first possibility, the second being lesions due to some bacterial focus, and as the third, the rather remote possibility of factitial dermatitis. Because of the possibility that this is a self-induced eruption, I suggest a psychiatric study.

DR FRED WISE: I want to ask Dr. Andrews whether the diagnosis of dermatitis venenata is to be considered in association with a deep-seated subcutaneous induration.

DR GEORGE C. ANDREWS: Yes.

DR FRED WISE: I can conceive of the superfluous tissue's being removed by an experienced plastic surgeon with favorable ultimate cosmetic result.

DR HERMAN SHARLIT: Strangely, that impressed me as a good suggestion. Of course, if there is an infection present, it would be dangerous to perform an operation. But if one performs several cultures of the skin by the proper technic and pathogens are not isolated, I see no reason why it should not be attempted.

DR HOWARD FOX: I should consider this a classic case of solid edema of the face. Possibly one of the sulfonamide drugs might be helpful, as Dr. Costello suggested. I am extremely skeptical about the value of vaccines for this disease, having personally used them with no favorable results.

DR E. WILLIAM ABRAMOWITZ: If a patient has attacks of fever with recurrence of the eruption, which is the classic syndrome, the sulfonamide compounds may abort the febrile attacks and in some measure reduce the redness, but for patients who give no history of fever I think little can be accomplished with sulfonamide drugs or vaccines. I understand that this patient has had no febrile disturbances, and I question whether anything can be done with treatment except by a plastic operation.

DR DAVID BLOOM: When the edema is solid and of long standing, there is, in my opinion, little benefit to be expected from sulfonamide compounds or from any similar drug, for one has to assume the presence of fibrosis. When there is disfigurement, surgical procedure is indicated.

DR ANTHONY C. CIPOLLARO: I agree with the diagnosis. My experience with this disease is extremely limited; I have treated only 3 patients who had it, with no improvement by any method of therapy.

DR JACK WOLF: I told this man that I did not believe that anything could be done for him. He has had low voltage roentgen therapy and a long period of treatment with sulfonamide drugs, all without benefit. We thought of removing the redundant tissue from the eyelid, which is largely responsible for the unfortunate appearance, but, since the edema is secondary to the process involving the cheek, it is doubtful whether this operative procedure would offer more than a temporary respite. The patient tells me he had a pressure bandage made which he applies at night and which fits snugly. Unless he wears this, the edema is much worse. The pressure exerted by the bandage forces some of the fluid back and reduces the swelling.

### Lupus Erythematosus of Unusual Type Presented by DR MAURICE J. COSTELLO

Miss E. C., a woman aged 36, from private practice, acquired her first lesion on the chest about two years ago. This disappeared in six months without treatment. Six months ago several lesions recurred, there was one lesion on the right lower eyelid half the size of a dime and smaller lesions on the left upper eyelid, the left superciliary region and the upper right pectoral region. The patient stated that she had received three roentgen ray treatments prior to her first visit to me, one on July 2, another on July 9 and the last on July 16, 1943, without effect on the lesions. On October 21 she was given an injection of 1 cc of bismuth subsalicylate in oil and 3 cc of crude liver extract. An ointment in a vanishing cream base containing 10 per cent phenyl salicylate was also prescribed, and she was cautioned about undue exposure to sunlight. On October 30 she received injections of bismuth subsalicylate and crude liver extract. The eruption appeared to improve, and the injections were repeated on November 6. On November 13, there was an increase in redness and edema which the patient attributed to undue exposure to artificial light. On November 20 there was intense edema of a quarter-sized area surrounding the lesion on the right lower eyelid, with crusting and oozing. A wet compress was prescribed. A blood count at that time showed 7,250 leukocytes, of which 60 per cent were neutrophils, 36 per cent lymphocytes, 2 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The erythrocyte count was 4,150,000, the hemoglobin content 76 per cent and the color index 0.9. A roentgenogram of the chest did not give any indication of pulmonary tuberculosis, although the patient stated that her sister had died of this disease.

On November 27 the patient stated that she had been taking a preparation of liquid petrolatum containing phenolphthalein. It was thought that this might account for the superimposed fixed eruption. Liver extract and bismuth subsalicylate were again injected. The eruption continued to increase in a centrifugal manner. On December 4, there was a sharply circumscribed silver dollar-sized lesion involving the upper eyelid, lower eyelid and malar prominence. Its border was elevated and studded with widely spaced crusted papules. There was a flare-up of the lesions of the left eyelid and the right upper pectoral region. The centers of these lesions, the sites of the original ones observed, were now white and surrounded by intense erythema. An intravenous injection of 125 mg of gold sodium thiosulfate was administered.

On examination today the eruption is definitely improved. The margin of the lesion on the face previously described is barely visible, and the intensity of the reaction of the lesion on the chest has ameliorated. The patient was given 25 mg of gold sodium thiosulfate intravenously this afternoon.

#### DISCUSSION

DR E. WILLIAM ABRAMOWITZ: The lesions are unusual, especially the history of edema and rapid spreading. That might happen under activation from treatment. From the lesions on the eyelid, I should make a diagnosis of lupus erythematosus.

DR MAURICE J. COSTELLO: The patient reported after an exacerbation that she had been taking a laxative containing phenolphthalein. I thought that the lesions of lupus erythematosus acted as the point of least resistance.

DR FRED WISE Dr Costello's idea that the eruption might be aggravated by phenolphthalein is more logical than the opinion that it might be made worse by bismuth.

DR E WILLIAM ABRAMOWITZ I think that either the bismuth or the gold used in treating the patient is more apt to cause this type of eruption than phenolphthalein. One of the things that Jadassohn emphasized regarding the fixed eruption was that it usually occurred in previously normal skin.

DR MAURICE J COSTELLO Within a period of four weeks the patient acquired an eruption on the right side of the face which had an elevated, sharply margined advancing border, with central clearing. To my mind this is unusual for lupus erythematosus. I do not recall ever having seen such an example before. The eruption remained stationary for a long time, accompanied by intense redness of all areas involved. After the use of phenolphthalein was discontinued, the edema was still intense the following week. The exacerbation occurred within forty-eight hours after the patient had received bismuth or liver. I should say that it was probably the liver that caused this, because two weeks ago when I gave the patient 125 mg of the gold salt and omitted the injection of liver extract the eruption subsided and practically disappeared.

#### A Case for Diagnosis (Pityriasis Rosea? Lichen Planus?) Presented by DR MAX SCHIFFER

I S., a woman aged 33 registered at the New York Skin and Cancer Hospital on Dec 9 1943, presenting cutaneous lesions of one month's duration. A pinpoint-sized spot first appeared on the middle of the volar surface of the right forearm. Within a week other lesions developed on the forearms, the inner surfaces of the thighs, the buttocks, the popliteal areas and the back of the neck, in the order given. The general health has been unaffected. The lesions are slightly pruritic, more so at night.

The lesions are symmetric and consist of pinhead-sized to match head-sized purplish papules, best seen on the dorsal surfaces of the hands and volar surfaces of the wrists. Most of the lesions are located on the lower part of the back and buttocks, where they are diffusely involved and few clear areas are seen. The patches here are irregular, poorly defined, of various shapes and sizes, finely wrinkled and covered with fine scaling. Some are oval, with accentuation of the borders and clearing centers. Diascopic pressure causes only partial fading of the lesions. The oral mucosa is not involved.

Examination of the scrapings for tinea was unsuccessful. Two sections were removed from the thigh for histologic examination, which was performed by Dr Charles F Sims. The epidermis presented a mild and slightly irregular acanthosis with some areas of parakeratosis. At some points, interstitial edema of the lower part of the epidermis could be noted, associated with exocytosis. There was a mild interstitial and parenchymatous edema of the collagen in the papillary zone. The vessels of the upper portion of the corium were moderately dilated and surrounded by a sparse cellular infiltration composed for the most part of small round cells. The differential diagnosis from this section lies between parapsoriasis and pityriasis rosea. The meager abnormalities in the section, such as a spotty parakeratosis, exocytosis and subepidermal edema, are common to both diseases. The absence of a true subcorneal vesicle, however, favors the diagnosis of parapsoriasis.

#### DISCUSSION

DR ISADORI ROSEN I think Dr Scheer's first diagnosis is correct, namely, pityriasis rosea with secondary dermatitis. The unusual feature is the profuse eruption below the waistline.

DR GEORGE C ANDREWS I agree, but there is a dermatitis superimposed on pityriasis rosea.

DR MAX SCHIFFER I agree, of course, with the diagnosis of pityriasis rosea, though in daylight one sees that there are some lichenoid lesions on the forearm. There are no typical lesions of lichen planus. The biopsy suggested parapsoriasis.

#### Adenoma Sebaceum Presented by DR HERMAN SHARIT

H M., a white man aged 47, has had small growths on the face, nose and forehead for over twenty years. These have slowly become larger.

On these areas the patient now presents flesh colored globular masses ranging from the size of a pea to that of a small marble. These are not painful.

At the time of presentation a tentative diagnosis of adenoma sebaceum was made. Subsequent study of a biopsy section revealed the eruption to be trichoeplithoma.

#### DISCUSSION

DR WILBERT SACHS It is a nevroid disease in which one may find any one of many tumors such as trichoeplithoma, cylindroma and adenoma sebaceum.

DR HOWARD FOX I agree that the lesions are much harder than those of adenoma sebaceum and that they closely resemble lesions of the scalp causing what is called the turban tumor.

DR MAX SCHIFFER I should defer therapy until the histologic report is obtained.

DR E WILLIAM ABRAMOWITZ I think that roentgen therapy in a limited area might be worth trying especially if the histologic report is that of a form of benign epithelioma.

DR JACK WOLF I agree with the idea of getting a histologic section and establishing a definite diagnosis before attempting therapy. Many of the pedunculated lesions can be ablated and the patient's appearance considerably improved.

DR DAVID BLOOM The term "adenoma sebaceum" is usually used as a synonym of epiloia, or Pringle's disease. Frequently, however, it is meant to designate adenomatous changes in the sebaceous glands, as seen in the aged, or belonging to nevus, as in this patient. The term is therefore confusing.

DR GEORGE C ANDREWS I agree with Dr Sachs and think it might be benign cystic epithelioma.

DR D E H CLELAND, Vancouver, British Columbia, Canada (by invitation) It seems to me that the lesions about the external meatus and also a few on the sides of the neck are similar to those seen in adults after acne, which may be clinical grounds for agreeing with Dr Sachs's opinion.

DR HAROLD ORR, Edmonton, Alberta, Canada (by invitation) I have never seen adenoma sebaceum develop in an elderly person. Electrodesiccation would probably be a satisfactory method of treatment.

DR GEORGE M LEWIS This man was a patient at New York Hospital eight or ten years ago. A biopsy was made, but, unfortunately, the record and the block of tissue cannot be found. At that time the lesions were much smaller than tonight.

DR FRID WISE I agree with those who say that there should be no attempts at therapy until the histologic diagnosis is established, but I think that the absence of vascular lesions speaks against a diagnosis of adenoma sebaceum

DR WILBERT SACHS One cannot differentiate microscopically among sebaceous nevus, adenoma of the sebaceous glands and adenoma sebaceum

DR HERMAN SHARLIT I was of the opinion that this is a nevus and that the appendages of the skin are involved, particularly the sebaceous glands. Only a histologic examination can reveal the exact diagnosis

#### Scleroderma Presented by DR GEORGE C ANDREWS

A E, a nurse aged 36 was well until a short time after she had "virus" pneumonia in February 1943. At this time she noted a dull pain in the joints of the hands and feet and swelling of the right forearm and wrist. The swellings became indurated and widespread. For twenty years she has had a chronic pansinusitis. Seven years ago she had one ovary and part of the other removed, but the menses have remained normal.

Examination reveals a symmetric brawny induration of the skin and subcutaneous tissue of the forearms, arms, shoulders, upper part of the chest and breasts. The lower extremities are mildly edematous, and on the thighs there are streaks of induration. The hands, abdomen, axillas and face are normal. The involved areas show a mottled light brown to dark brown pigmentation. The hands are warm and show no changes such as are seen in Raynaud's disease.

Early in the course of the disease the patient was given ovarian preparations and thyroid extract. For the past three months she has had subcutaneous injections of 1 cc of neostigmine methylsulfate (1:2,000) daily, along with 15 mg of neostigmine bromide and 25 mg of papaverine hydrochloride three times a day by mouth. There has been no improvement.

Although the patient lacks the vasomotor and trophic symptoms of acrosclerosis, the onset with arthritis and the persistent arthralgia make this diagnosis possible, although the absence of Raynaud's symptoms, the short duration, with spreading to body and thighs, and the lack of involvement of the face are against this diagnosis.

#### DISCUSSION

DR FRID WISE The patient has the ordinary variety of progressive scleroderma, and I believe that the name "acrosclerosis" should be used only when the scleroderma begins at the fingers and progresses upward.

DR HOWARD FOX I doubt whether there is any myositis in this case on account of the absence of tenderness. I exerted firm pressure on the lesions without causing any pain.

DR JACK WOLF I agree with the diagnosis of scleroderma. I wonder whether many cases of Scleroderma are not examples of Raynaud's disease.

DR DAVID BLOOM A distinction can be made between scleroderma and acrosclerosis. The latter disease starts with involvement of the fingers, toes and face. Later, lesions may develop on the body. Progressive symmetric scleroderma is in my opinion, more serious than the other forms of scleroderma.

DR PAUL GROSS (by invitation) This is an interesting case for differential diagnosis. In examining the patient one could feel a rather deep-seated infiltration like that of scleroderma adultorum. The eruption developed after an acute infectious disease, and the histologic changes are not typical of scleroderma. I should like

to inquire of Dr Fox whether, despite the atypical location, the diagnosis of scleroderma adultorum would not be justified. The possibility of a recurrent panniculitis can be excluded on the basis of the histologic changes.

DR HAROLD ORR, Edmonton, Alberta, Canada (by invitation) I think that this is the ordinary variety of progressive scleroderma.

DR MAURICE J COSTELLO I think that this patient has scleroderma and believe with Dr Rosen that she also has myositis. Most of these patients give a history of being unable to walk without severe pain in the calf muscles unless they walk on their toes. I should like to offer a suggestion as to therapy, because one of my patients was definitely helped by dihydrotachysterol in fairly large doses.

DR ANTHONY C CIPOLLARO I agree with the diagnosis of scleroderma and suggest a combination of chemotherapy and physical therapy, the latter by way of the whirlpool bath to produce hyperemia by heat and massage, and chemotherapy to produce vasodilatation, by intravenous injections of mecholyl chloride or sodium nitrate.

DR WILBERT SACHS I want to disagree with the conception of fibrinoid degeneration in scleroderma. I have never found it or any other tinctorial degeneration in which the tissue is entirely absorbed.

DR GEORGE C ANDREWS As Dr Costello remarked, this woman has great pain in the legs, so that she stumbles and falls. It may be due to myositis of the posterior tibial muscle. I think one should go further into the matter of dermatomyositis.

#### A Case for Diagnosis (Lupus Erythematosus and Granuloma of the Lip?) Presented by DR ANTHONY C CIPOLLARO

G H, a white man aged 59, born in Ireland, first attended the New York Skin and Cancer Hospital on June 28, 1939. He was previously presented at the New York Academy of Medicine on Oct 3, 1939 for diagnosis, the possibility of tertiary syphilis, moniliasis and lupus erythematosus being considered.

The patient had a penile lesion of syphilis in 1917, for which he was treated for three and one-half months. Then for some unknown reason the treatment was stopped. About five years ago therapy was resumed, and he was treated continuously with alternate courses of arsenicals and bismuth preparations for a period of two and one-half years.

The Wassermann reaction of the blood and spinal fluid has always been negative.

In August 1934, the patient was badly sunburned at the beach and the lower lip became swollen. Fissures developed the following day. In spite of much treatment with various topical remedies, including roentgen rays, and fever therapy (typhoid vaccine), the eruption persisted.

A recent complete medical check-up, including an examination of the spinal fluid and roentgen examinations, revealed normal conditions except for the local lesion. On the basis that the lesion might be of syphilitic origin, the patient was given two courses of a bismuth preparation and three courses of neoarsphenamine, with slight changes in the lesion of the lip but never with complete remission.

A Frei test was performed, and found to elicit a positive reaction, it was then thought that the lesion was an unusual manifestation of lymphogranuloma venereum. The patient was treated with Frei antigen and also with fuadin, without improvement.



Several biopsies were performed, with the following reports

July 5, 1939 "Superficial dermatitis with pronounced cellular infiltration, predominantly plasma cells"

May 8, 1940 "Suggests a syphiloderm"

May 19, 1941 "Tertiary syphilis"

Nov 11, 1942 "Prickle cell epithelioma"

Dec 1, 1942 "Chronic inflammation of the skin and mucous membranes"

All of these tissues were removed from the lip

Various blood counts were normal. Determinations of sedimentation rate and of blood chemistry, tests of hepatic function, urinalyses and swabs for bacteriologic examinations all yielded essentially normal findings

The patient was thoroughly studied in the vascular clinic, and no evidence of vascular disease found

Since the patient was thought to have an epithelioma of the lip, he was referred to the tumor clinic, where he was watched and studied carefully, no evidence of malignancy of the lesion was found. He was treated there with blind local remedies and with large doses of compressed yeast

During the past few weeks several lesions have developed on the face and neck. He now presents a lesion on the lower lip affecting mostly the right side of the lip which is of a granulomatous nature, with some depression and some superficial ulceration. There is a granulomatous process which is probably inactive at present. On the sides of the face and neck there are scaly erythematous lesions, sharply demarcated and somewhat telangiectatic, suggesting the possibility of lupus erythematosus

#### DISCUSSION

DR DAVID BLOOM I have been impressed with an observation which I have made of 3 or 4 patients with lupus erythematosus of the lips or near the lips, namely, the atypical appearance of lupus erythematosus in this area. I believe the patient has lupus erythematosus of the chin

DR HOWARD FOX I think that this man is suffering from two diseases. He obviously has had syphilis, but I cannot conceive of the lesions on the neck being a late manifestation of syphilis. They are certainly not nodules. A diagnosis of lupus erythematosus was made early in the course, hence that diagnosis is a likely one.

DR WILBERT SACHS The slide I saw from the lip was definitely not a section from a lesion of lupus erythematosus. My diagnosis was syphilis.

DR FRID WISL I examined this patient three years ago, at which time he had a syphilitic lesion, confirmed by biopsy, on the lower lip. He now shows a syphilitic tongue, with leukoplakia and atrophy of papillae, and the lesions of lupus erythematosus on the sides of the neck. I believe that if this patient were demonstrated as having lupus erythematosus and nothing were said about the other lesions, it would be agreed that the eruption on the side of the neck is lupus erythematosus. I see no reason why the two diseases should not coexist on different parts of the body.

DR E. WILLIAM ABRAHAMOWITZ We had this patient in the hospital and were never able to make any kind of clinical diagnosis for the lesions of the lip, aside from the fact that he had signs of syphilis of the tongue and had had inadequate antisiphilitic treatment. Rather strenuous antisiphilitic treatment had only a slight influence on the lesion. He later acquired an ulceration on the mucosal side of the lip for which a diagnosis

of prickle cell epithelioma and later chronic inflammation was made. I can say that this man has lupus erythematosus now. The lupus erythematosus of the lip may have had an unusual appearance because of his old syphilis.

DR PAUL GROSS (by invitation) Even if this patient has lupus erythematosus and leukoplakia of the tongue, he also has a perlèche-like lesion at the corners of the mouth and vascularization of the cornea. I believe that intensive therapy with parenteral injections of liver extract and riboflavin will be of benefit.

DR MIRIAM B. PAROUNACIAN I do not know what the eruption was previously, but the present eruption especially the lesions behind the ear, are not syphilitic and I favor a diagnosis of lupus erythematosus.

DR ANTHONY C. CIPOLLARO I think Dr. Wise adequately summarized the case. The man had syphilis, and now has syphilis and the lesions on the neck are lesions of lupus erythematosus. He has received liver and vitamin therapy and I think, in adequate dosage.

#### Dermatitis Medicamentosa (Bromide? Iodide?) Superimposed on Rosacea Presented by DR GEORGE M. LEWIS

M. B., a 29 year old housewife is presented from the New York Hospital. She first had rosacea two years ago. Until recently she has drunk thirty cups of tea each day. The skin has been treated by topical applications. Recently she consulted another local physician, who prescribed a 'nerve medicine' iodized salt has been used at home for years. Three weeks ago blisters appeared on the face and the areas of rosacea became more prominent. At present there are erythematous, elevated, succulent and exudative papules and papulopustules on the chin, nose and inner surfaces of the cheeks. These lesions are on the sites previously affected with rosacea.

#### DISCUSSION

DR E. WILLIAM ABRAHAMOWITZ I believe the diagnosis of bromoderma is correct. It is common for such an eruption to be localized to areas of trauma. I presented a patient before this society several years ago who took bromides concurrently with injections of insulin and in whom bromoderma appeared in the exact locations of the injections of insulin.

#### Onychomycosis, Erosio Interdigitalis Blastomycetia Presented by DR GEORGE C. ANDREWS

C. J., a Negroess aged 49, has an eruption of the hands of several months' duration. She is a domestic and has her hands in water much of the time. There is a family history of diabetes mellitus.

Examination reveals a scaly erythematous dermatitis of the webs and opposing surfaces of the fingers. The paronychia tissue of all fingers is red and swollen. The finger nails are discolored and ridged and are detached from the nail bed in some areas.

Sodium hydroxide preparations of scrapings from the finger nails and from the skin between the fingers showed hyphal threads with budding cells. Cultures are being studied. The blood sugar level was normal.

#### DISCUSSION

DR GEORGE M. LEWIS I think that this is an unusual case. I wonder how often one sees moniliasis of the nail without a chronic paronychia. Furthermore, the nails appear to be infected distally rather than proximally, perhaps this is due to exogenous infection.

LOS ANGELES DERMATOLOGICAL  
SOCIETYWILLIAM H GOFCKERMAN, M D, *Chairman*CLEMENT E COUNTER, M D, *Secretary*

Jan 11, 1944

## A Case for Diagnosis (Contact Dermatitis?) Presented by DR CLEMENT E COUNTER

H S, a man aged 48 years, observed the onset of the present dermatitis of the face, neck and right hand on Sept 11, 1943. Since then the lesions have been continuous. He had to cease work. In spite of various treatments there has been no improvement at any time since its onset. There have been many previous attacks for the past twenty years. The patient had some asthma during boyhood.

The face is red and swollen, with a tendency to crusting and fissure formation. On the chin and cheeks are numerous discrete round smooth papules about 3 mm in diameter. These are crowded together on the chin and are more widely separated on the cheeks. The backs of the hands and forearms are also red, crusted and fissured. There are no other lesions on the body. The right hand and right forearm are more involved than the left.

The Wassermann reaction of the blood was negative. The hemoglobin content was 88 per cent, there were 4,730,000 erythrocytes and 15,000 leukocytes, of which 58 per cent were neutrophils, 10 per cent monocytes and 13 per cent eosinophils.

## DISCUSSION

DR SAMUEL AYRES JR I thought that this case was an example of atopic eczema. The patient also had some asthma and hay fever. The distribution of the eruption is characteristic, and he has had it for years.

DR L F X WILHELM I agree with Dr Ayres. I questioned the patient rather closely, and he said that he had had asthma until he was 12 or 13 years of age. He has had this disease for twenty years.

DR A FLETCHER HALL I thought it was of some significance that the first attack of dermatitis occurred when he was a photoengraver, working with ammonium dichromate, about twenty years ago. He stopped that work and operated a filling station for a year, during which time the dermatitis cleared. He went back to photoengraving again, he came into contact with ammonium dichromate and has had trouble ever since. He has been in some similar type of work ever since. He now uses neither blueprints nor photoengraved prints but he handles silver prints. I do not know what these are, but almost all printings and copying processes involve the use of some chromate. He is now working at a shipyard as an expeditor. Although he does not actually handle production materials, his work takes him pretty well all over the plant and he may contact many unsuspected materials. I think that this is a contact dermatitis instead of or superimposed on an atopic dermatitis. It may be found that he is having some contacts with chromates or chromic acid. This recent flare-up may well be due to such contact.

DR NELSON PAUL ANDERSON I agree with Dr Hall. I feel there is a definite contact element in this eruption. The man does not have a true clearcut picture of atopic dermatitis. He has involvement of areas that one finds in atopic dermatitis but which are also involved in contact dermatitis. There is a certain type of atopic der-

matitis and possibly of contact dermatitis in which a peculiar atrophy occurs, with fissuring and radial linear creases in the lips. This man has this to such a degree that if he were to be cured tomorrow he would retain the marks of fissuring about the mouth which one sees in congenital syphilis. I am certain that this is not an ordinary atopic dermatitis.

DR M E OBERMAYER Did you say, Dr Anderson, that the man showed changes which you thought were atrophy?

DR NELSON PAUL ANDERSON I think he has definite atrophy of the upper lip.

DR M E OBERMAYER I do not think that true atrophy is present. The changes are, rather, hyperplastic, and the loss of elasticity of the skin accounts for the fissured appearance, which simulates the perioral radial scars of prenatal syphilis.

DR CLEMENT E COUNTER The patient has been away from his work entirely for at least three months, and for two weeks of that time he was confined to a room in which there was only the minimum amount of bare furniture. In this way conditions were simulated which are used in the treatment of asthma. Even these measures achieved no improvement. Food tests did not reveal any additional information. I think that it is neither a clearcut dermatitis nor yet a well defined atopic eczema.

## A Case for Diagnosis (Cysts of the Eyelids?) Presented by DR SAMUEL AYRES JR

J B, a man aged 57 years, complains of swelling of both upper eyelids, which was first noticed about two or three months ago. He stated that swelling is sometimes more prominent in one eyelid than the other. Occasionally the swelling recedes a little, but it has never disappeared. The patient donated blood to the blood bank three times between January and September 1943, and he states that the present eruption began after the last donation.

The eruption is limited to the medial aspects of the upper eyelids and consists of a diffuse, somewhat oval area of soft swelling, giving the appearance almost as though there were a cyst beneath the skin. Palpation, however, reveals the swelling to be soft and compressible. No redness was observed. There are no abnormalities elsewhere about the eyelids or elsewhere on the skin. There is no edema of the legs, and no lesions are present on the scalp.

A complete blood count showed erythrocytes, 5,260,000, leukocytes, 8,700, hemoglobin content, 100 per cent, color index, 0.96, neutrophils, 68 per cent, monocytes, 7 per cent, lymphocytes, 23 per cent, and eosinophils 2 per cent. Urinalysis showed a faint trace of albumin, but the urine was otherwise normal.

Microscopic examination revealed very few pus cells and red blood cells and few epithelial cells.

## DISCUSSION

DR A FLETCHER HALL I could not see that this is a dermatologic disease, I thought that there was something subcutaneous or on the under surface of the eyelid.

DR KENDAL FROST I believe that this lesion is a small subcutaneous tumor. If the eyelid is lifted up, it can be seen protruding under the palpebral conjunctiva. It suggests a bilateral cystic condition.

DR ROGERS WAKEFIELD The swelling appears to be under the conjunctiva, and when the eyelid is pulled



forward it seems to connect with the sclera. When it is pressed downward one feels a soft cystic mass. The patient states that the swelling is often much smaller in the early morning.

DR JOSEPH MIROVICH (by invitation) It suggested a myxedematous enlarge to me. It is unlike anything I have ever seen.

DR SAMUEL AYRES JR. Frankly, I have never seen anything like this before. The patient was referred to me by an eye, ear, nose and throat specialist. The disease presented an entirely new picture to me. While the growth looks cystic, it does not feel cystic. It is completely soft and compressible. The fact that it is bilateral and developed simultaneously on both sides would argue against a cyst.

**A Case for Diagnosis (Rosacea-Like Tuberculid of Lewandowsky?)** Presented by DR SAMUEL AYRES JR.

H. H., a woman aged 46 years, has had an eruption of the face for about one year. It has gradually spread, especially, during recent weeks. There has been no previous treatment.

The eruption is limited to the face, involving the medial aspects of the cheeks, nose, chin and forehead showing diffuse redness with tiny, pinhead-sized, slightly elevated papules with reddish points but no definite pustules or vesicles. Under pressure with a glass slide the lesions have a definite apple jelly appearance.

A general physical examination showed no abnormalities.

The reaction to a tuberculin patch test applied for forty-eight hours was negative at the time four days had elapsed, but eleven days after tests were applied both dilutions had elicited strongly positive delayed reactions, which the patient first observed on the ninth day after tests were applied. The reaction resembled closely the eruption on the face, consisting of punctate, almost hemorrhagic macules with a surrounding yellowish pink color which persists under pressure with a glass slide. Diagnostic roentgenograms of the chest revealed calcified lymph nodes but no active tuberculosis.

DISCUSSION

DR A. FLETCHER HALL I thought that I could demonstrate some tubercles on diascopy, and I agree with the diagnosis of rosacea-like tuberculid of Lewandowsky.

DR KINDAI FROST I agree with the diagnosis.

DR M. E. OBIRMAIR I thought that the eruption was a classic example of Lewandowsky's tuberculid.

DR SAMUEL AYRES JR. An interesting feature of the case is the greatly delayed tuberculin reaction. Patch tests with tuberculin left on forty-eight hours elicited no signs of reaction until nine days after the test was applied, when the reaction developed. On the eleventh day the reaction was strongly positive. The reaction was identical with the eruption on her face. I should like to raise the question of therapy. This patient has been examined by an internist in the past year, the examination including roentgenograms of the chest. The internist was of the opinion that tuberculin therapy would be particularly indicated for this patient. I am wondering if any of the members have had experience with the use of tuberculin subcutaneously in the treatment of such an eruption.

DR MAURICE NORRIS Dr Anderson and I presented a patient before the society two years ago with the same

type of eruption. We diagnosed it Lewandowsky's syndrome. He was given tuberculin for a considerable time, with no improvement.

**A Case for Diagnosis (Erythema Annulare Centrifugum?)** Presented by DR H. C. L. LINDSAY

I. S., a woman aged 50 years, has a delicate white skin. There are erythematous circles on the skin of the abdomen, below the left breast and over the right nipple. These lesions are of various sizes and are almost complete circles, as if stenciled with a fine red pencil guided by a compass. The enclosed skin appears normal. There is no induration of the red lines. These lines disappear on diascopic pressure. The laparotomy scar interrupts the completeness of one circle. The line is absent in the scar but continues on the opposite side symmetrically. The lesions have been present twenty-eight days. The color is fading rapidly now.

The patient thinks that she has adhesions and intestinal stagnation. Roentgenograms showed no gallstones. She has much flatus. The patient has had a great deal of intestinal disturbance since she had her cecum removed, in 1922. She has had chilly sensations across the legs and back for a long time.

DISCUSSION

DR A. FLETCHER HALL I questioned this woman about drugs taken. She says she has taken "Nature's Remedy" almost all her life, but about three weeks prior to the onset of the eruption she got a new box of it and noticed that the pills were a little different in color. I think that the diagnosis of drug eruption should be entertained.

DR NELSON PAUL ANDERSON I think that I have seen about 6 such cases, and in all of them there were associated pathologic changes in the urinary tract. This woman gives a history of a low grade pyelitis, which she associates with an upset bowel. At various times albumin, sugar and other abnormal constituents have been found in the urine. I think that it would be worth while to check a catheterized specimen of urine. It might be of value to give her a sulfonamide compound internally. I think that the eruption would then disappear quickly.

DR H. C. L. LINDSAY The patient's skin is clearing so fast that I do not believe that I shall be able to give her any medicine with this attack.

**A Case for Diagnosis (Neurotic Excoriations?)**

Presented by DR IRVING R. BANCROFT

P. C., a single man aged 27, presents an eruption on his face and neck.

The history reveals that he fell when he was an infant and was severely burned on the face and neck. He was treated with lime liniment, N. F. and other soothing medications for a period of six months.

When he was 17 years old, he had comedos and a few pustules. He was treated with various ointments and fell into the habit of picking his face when he was asleep and has continued that habit up to now.

He was at the Mayo Clinic for six weeks in 1938 and was discharged well, but he was told that the apparent cure was temporary and that he should go to Tucson, Ariz., and no other place. He went to Tucson and remained well while he stayed there. He came to Los Angeles and immediately became worse. He picks the lesions while asleep.

Allergy tests showed sensitivity to chocolate, pork and orris root

## DISCUSSION

DR PAUL D FOSTER This is the type of eruption I have always considered to be an atopic eczema with a seborrheic background. It has always seemed to me that in such cases there is a mild pyogenic infection such as one finds in seborrheic dermatitis.

DR H C L LINDSAY It is partly seborrheic dermatitis, and the patient picks at it constantly, so that the neurotic factor is present also.

DR M E OBERMAYER The diagnosis of neurotic excoriations does not appear justified. Dr Foster is correct in stating that this patient had a chronic dermatitis. My diagnosis is dry neurodermatitis with excoriations. The term "neurotic excoriations" should be limited to eruptions in which the only cutaneous changes are excoriations in their various stages, unaccompanied by dermatitis.

DR NELSON PAUL ANDERSON I think that this is an example of neurotic excoriations.

DR SAMUEL AYRES JR Is there not a history of rather long-continued trouble? This goes back fifteen years. There may be an element of nervousness there, but there must be an atopic background.

DR W H GOECKERMAN I, too, think the man has definitely a dermatitis. The excoriations are simply secondary to the pruritus. To me the dermatitis is evident right now.

DR IRVING BANCROFT This man does not have exactly a seborrheic skin. In fact, he complains of its being extremely dry. A peculiar thing is that when he was at the Mayo Clinic the skin cleared perfectly. He was told to go to Tucson, and when he did so it cleared. Then he came to Los Angeles, and the eruption recurred. He apparently does not want to go into the Army, and he is extremely sensitive and scratches his face while asleep. When there are any lesions on his face, he will not go to work. It seems to me possibly a psychiatrist could do him some good.

#### A Case for Diagnosis (Acrocyanosis?) Presented by DR SAMUEL AYRES JR

I D, a man aged 21 years, has one brother with a similar disease. There has been redness of hands, feet, ears and face of about ten years' duration. The discoloration has been continuously present, but it is worse in cold weather. The patient has always lived in California and so far as he knows has never been frostbitten.

At present his hands and wrists are continuously red. They are congested and cold. The palms are wet with perspiration. The feet present a similar appearance but less pronounced. The front of the cheeks and the rims of the ears also show congestion. The anterior aspect of the rims of the ears show four or five pinhead-sized whitish nodules.

This case is presented for discussion of causation and for suggestions as to therapy.

The pulse rate is persistently 92 to 98, but the pulse is regular and full.

## DISCUSSION

DR SAMUEL AYRES JR This man presents a real problem. The family physician referred him to me one year ago, and I made some suggestions about checking up on his circulatory condition. One week ago I again suggested a determination of the basal metabolic

rate and an electrocardiogram, but apparently this has not been done. He has had this eruption for six or seven years. He has always lived in California and has never been frostbitten. He always has this reddish, purplish appearance and flushing of the rims of the ears. There must be some peculiar circulatory disturbance. I thought he would have a slow pulse, but the rate was 92 and 98 on two occasions. I thought that the man should have some rather careful studies, but they have not been made. Apparently it is a rather uncomfortable condition to have and somewhat embarrassing. This case is one of those in which internal medicine and dermatology overlap.

#### A Case for Diagnosis (Lichen Planus, Tinea Circinata, Seborrheic Dermatitis?) Presented by DR ANKER K JENSEN

W E D, a woman aged 28 years, began to have an eruption about two weeks ago. It first appeared on the lower part of the back over the left buttock. This has extended down over the left thigh and to the anterior surface of the left leg. There has been a moderate amount of itching in this area. The whole process followed the birth of her child. There has also been an eruption on the pubic area and scalp for the past fourteen years which has not given her much discomfort. She states that about once or twice a year she has another type of eruption that usually lasts about three weeks and disappears. This is also present tonight.

There are grouped papular lesions on the left buttock, left thigh and left leg. These are flat topped and of a violaceous color. Some of the patches are the size of a palm. Some are linear, and there are numerous scattered circinate lesions on the extremities and on the trunk. There is central clearing with a slightly raised scaly border. No vesicles are present tonight. There is also an erythematous scaling eruption in the pubic area and thickened crusted lesions on the scalp.

## DISCUSSION

DR ROGERS WAKEFIELD This woman presents two or three different types of lesions. The one on the front of the scalp looks like an excoriated patch of seborrhea or psoriasis. Then those lesions that started on the front of the left thigh have merged into one large plaque, while those laterally down the leg seem to be composed of closely grouped erythematous papules with heavy scaling. Some of the healing lesions look as though they might have been vesicular at the first, but the patient said no lesion had ever exuded liquid. I could not find any papules resembling lichen planus. The whole picture looked to me like a rather peculiar distribution of a seborrheic dermatitis.

DR M E OBERMAYER I think that this interesting eruption is not lichen planus but linear psoriasis. Linear psoriasis, linear lichen planus and lichen striatus may look much alike clinically, but since there is evidence of psoriasis on other parts of the body it does not seem justified to assume the presence of two different papulo-squamous eruptions in one person. Biopsy of one of the linear lesions would settle the diagnosis.

DR SAMUEL AYRES JR The patient says that she has had these ringlike lesions all of her life. I thought they looked much like erythema annulare centrifugum. Some were small, others had widened out into thin-bordered circles. She says the eruption in her crotch has been present for ten years. Perhaps that is psoriasis, but this acute process on the left thigh and

buttock has been present only two weeks. It is continuous, however, with the eruption in the groin. That certainly does not look like psoriasis, and if one has to consider only one area it looked like a contact dermatitis from scrubbing with soap and water, but even that cannot account for the whole picture.

DR NELSON PAUL ANDERSON. I think a great deal of discussion could be avoided if Dr. Jensen would perform a biopsy.

DR W. H. GOECKERMAN. I, too, should like to consider all these lesions as psoriasis, although, as Dr. Anderson says, a biopsy is desirable.

DR PAUL D. FOSTER. Several years ago Dr. McKee and I had a patient in New York with an eruption similar to this one. It would clear completely and then develop again in approximately the same form. Dermatologically it was psoriasis.

DR ANKER JENSEN. When I first saw this patient, the linear eruption on the thigh and leg was definitely made up of flat-topped discrete violaceous papules. Tonight many of these have coalesced and formed large plaques. Because of the strange appearance of this eruption, associated with totally different lesions, I called in Dr. Chris Halloran for his opinion. From clinical observation, we were both sure that it was lichen planus. The oval circinate lesions on the arms and body, we thought were erythema centrifugum, although they looked more like tinea circinata. Those in her scalp and over the pubic area we felt were psoriasis.

#### A Case for Diagnosis (Lupus Erythematosus of the Scalp?) Presented by DR. PAUL D. FOSTER

P. B., a man aged 40 years, was first seen on April 5, 1943. Then he gave a history of having had an eruption for about one and one-half years.

The patient presents shiny, bald, atrophic areas surrounded by erythematous areas with grouped follicles. The eruption started with one small area. New areas appear intermittently and grow in size.

The blood count revealed leukocytes, 8,850, erythrocytes, 4,680,000, hemoglobin content, 90 per cent, neutrophils, 68 per cent, lymphocytes, 24 per cent, large monocytes, 4 per cent, and eosinophils, 4 per cent.

The urine was normal.

The fasting blood sugar level was 100 mg per hundred cubic centimeters. The Kahn and Kolmer tests of the blood elicited negative reactions. A biopsy slide preparation is presented with the patient. Good results have been obtained from the thirty-nine weekly injections of bismuth subsalicylate and local application of solid carbon dioxide.

#### DISCUSSION

DR M. E. OBERMAYER. The clinical lack of scaling verified microscopically by the corresponding lack of parakeratosis as well as the absence of liquefaction necrosis of the basal cell layer make me hesitate to accept the diagnosis of lupus erythematosus.

DR SAMUEL AYRES JR. The patient stated that when the areas started, he had some pimples, there was nothing of that sort visible tonight, but there was a smooth atrophy. I did not see any plugging of the sebaceous orifices as in lupus erythematosus or any scarring. I thought of pseudopelade or folliculitis decalvans. I favor the diagnosis of pseudopelade.

DR PAUL D. FOSTER. This patient's eruption was rather typical of lupus erythematosus when he first came to the office, with the usual atrophic scaling associated

with lupus erythematosus. It has been only recently that the small areas of alopecia have developed. These areas are suggestive of folliculitis decalvans.

#### A Case for Diagnosis (Lupus Erythematosus of the Lips?) Presented by DR. PAUL D. FOSTER

G. B., a man aged 26 years, gives a history of impetigo and eczema as a child and he has had asthma since 6 years of age. Nine years ago he worked on an Indian Reservation in Arizona, and his present eruption has more or less prevailed since then.

There are nummular erythematous eczematized lesions on his arms. The lips show definite evidence of actinic cheilitis. They are excoriated, chapped and erythematous. The lesions on the lips have tight scales.

Hematologic examination revealed leukocytes, 8,700, erythrocytes, 5,500,000, hemoglobin content, 103 per cent, neutrophils, 69 per cent, lymphocytes, 27 per cent, monocytes, 1 per cent, eosinophils, 2 per cent, and basophils, 1 per cent.

The urine was normal. The blood sugar level was 96.8 mg per hundred cubic centimeters, the cholesterol level 172.0 and the Wassermann and Kahn reactions of the blood negative. The basal metabolic rate was 6 per cent plus.

A biopsy slide is presented with the patient.

#### DISCUSSION

DR KENDAL FROST. I agree with the diagnosis of lupus erythematosus of the chronic discoid type. I thought I could see a small area above the vermilion border on the left side of the upper lip where there was a small area of atrophy.

DR M. E. OBERMAYER. I agree with Dr. Frost. Histologically as well as clinically the lesion was lupus erythematosus of the lips.

DR SAMUEL AYRES JR. From a clinical point of view I think a diagnosis of lupus erythematosus is tenable, particularly from the way in which the lesions were rather sharply circumscribed. Yet the fact that both lips were affected made one consider the possibility of something else. I have seen lips very much like that associated with atopic dermatitis, and on quizzing the patient I found he had had infantile eczema for a number of years. While it is probable that this is lupus erythematosus of the lips, I suggest the possibility of atopic dermatitis.

DR PAUL D. FOSTER. It is interesting to note that the mother has pustular psoriasis of the palms and soles.

#### Tattoo Marks (to Demonstrate Methods of Removal) Presented by DR. PAUL D. FOSTER

D. C., a woman aged 29 years, had tattoo figures placed on both shoulders and on her right thigh when she was 13 years old. About four years ago these marks were worked on by the same type of machine as that used in their original production. Before that an attempt to remove the figure on the right shoulder had been made with local application of an acid.

Tattoo marks are present on the shoulders and on the anterior surface of the right thigh. All the images have been modified by treatment. The lesion on the right shoulder is almost entirely replaced by a scar, portions of which are hypertrophic. The lesion on the thigh is almost entirely removed with little scarring. Some of the original figure on the left shoulder lesion is still present unmodified.

## DISCUSSION

DR A FLETCHER HALL Before Dr Foster closes, I should like to have him clarify this point. The patient said that the lower tattoo on the leg had "the once over lightly", it looks like a better result than the one on the arm. I wonder whether you are using a different method and whether you can expect any better result than the one on the arm?

DR H C L LINDSAY In San Diego one surgeon uses a large cork with many needles projecting through it about  $\frac{1}{8}$  inch (0.3 cm). He pounds that part of the skin containing the tattoo and rubs in an acid, this produces a raw surface which crusts over, and when the crust drops off the spot is free from pigment.

DR ANKER JENSEN Dr Foster has had excellent results. I have used exactly the same method, and I can state that the use of a local anesthetic greatly facilitates the technique.

DR PAUL D FOSTER I presented this woman because she shows two stages in the removal of a tattoo. One area had already had two treatments, one had had one treatment, and one area had been untreated. It is my usual method to tattoo 40 per cent tannic acid into the lesion with electric tattooing needles. This is done thoroughly until the skin gives the appearance of soft sponge rubber. Then 50 per cent silver nitrate is painted over the area, forming a hard, black, adherent crust. The treated area is bandaged, and the crust is allowed to come off naturally. It usually takes two treatments to remove the tattoo completely. The advantage of this system over any other that I ever used is that the scaling is kept at a minimum. You probably noticed that the patient has a keloid on the left shoulder where some one had attempted to take off a mark with acid. Keloids have not developed in the areas treated with the electric tattooing needles.

#### A Case for Diagnosis (Mycosis Fungoides?)

Presented by DR A FLETCHER HALL

A N, a woman aged 40, has had itching plaques in the groins and on the sides of her neck near its base for the last six months. The eyelids became thickened and swollen at about the time of onset. She was found sensitive to the resins in a zinc chromate primer coat which she contacted when working in an airplane plant. The dermatitis was thought to be due to contact with this substance. After her transfer from contact with the resins of the primer coat, the eyelids improved but new areas of involvement appeared. Itching has been severe. The genitocrural area shows well margined brownish pink plaques on the anterior upper part of the thighs, there are similar plaques in the vaginal regions, on the inner upper surfaces of the arms and in the axillary regions. The extensor surfaces of the arms and of the feet show brownish pink to red, well margined slightly infiltrated plaques. A biopsy slide is presented with the patient.

Treatment has included the local application of five weekly fractional doses of unfiltered roentgen rays. Evolution of plaques and relief of itching followed.

## DISCUSSION

DR NELSON PAUL ANDERSON I do not know what this disease is. I think that the case requires a great deal of observation and perhaps repeated biopsies before one can make a definite diagnosis.

DR A FLETCHER HALL The circumstance that made the diagnosis doubly confusing in this case was that

the patient was a riveter in an aircraft plant, and when first seen complained of dermatitis affecting the eyelids and the sides of her neck, typical of that caused by resins in the chromate primer. She was found to be sensitive to the resins and was moved away from contact with them. Her eyelids cleared, but the dermatitis on the neck continued troublesome, and it became apparent that the dermatitis of the eyelids was in no way related to the lesions on the neck. Plaques then began to appear in the genitocrural area, and recently they have appeared scattered over the body. It may be that a biopsy of one of the lesions around the neck might show more characteristic conditions.

### NEW YORK DERMATOLOGICAL SOCIETY

A BENSON CANNON, M.D., *President*

GEORGE C ANDREWS, M.D., *Secretary*

*Jan 25, 1944*

#### Subacute Disseminated Lupus Erythematosus Presented by DR EUGENE F TRAUB

E deP, a married woman aged 25, entered the New York Post-Graduate Medical School and Hospital on Jan 3, 1944, with an eruption of five months' duration. The eruption was confined to the face, chest and flexor aspects of the digits. On consulting a dermatologist she was told to stay out of the sun and received two injections in her hip. With the development of swelling, stiffness and pains in the joints of the ankles, fingers and knees she was advised to enter the hospital. There has been intermittent diarrhea and constipation for the past year, the character of the stools not being noted. A spontaneous loss of 15 pounds (6.8 Kg) in weight has also occurred. The only medication she has taken has been Alka-Seltzer twice a week. (The label for this preparation states that each dry tablet contains acetylsalicylic acid, mono-calcium phosphate, sodium bicarbonate and citric acid and that in water this becomes sodium acetylsalicylate, calcium-sodium phosphate, sodium bicarbonate and sodium citrate.)

Examination shows patchy dime-sized areas of alopecia with erythema, scaling and telangiectasia. There is cervical lymphadenopathy. The heart and lungs are normal except for a soft systolic murmur at the apex. There is a diffuse erythematous scaly eruption involving the exposed areas of the body.

A roentgenogram of the chest was essentially normal. Roentgenograms of the teeth showed no periapical abscesses. A barium sulfate enema showed a moderate cecal ptosis and distention and hyperirritability and spasm of the distal portion of the colon. Roentgenograms of the sinuses and mastoids were essentially normal. The sedimentation rates were 36, 45 and 65 mm. There has been no elevation of temperature since her hospitalization. Erythrocyte counts and values for hemoglobin were respectively, 3,560,000 and 57 per cent, 4,280,000 and 67 per cent and 3,940,000 and 59 per cent. Leukocyte counts showed the following results: 5,300 leukocytes with 60 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, 22 per cent monocytes and 6 per cent eosinophils, 7,100 leukocytes, with 68 per cent polymorphonuclear leukocytes, 7 per cent lymphocytes, 22 per cent monocytes and 3 per cent eosinophils, 5,500 leukocytes with 66 per cent polymorphonuclear leukocytes, 6 per cent lympho-

cytes, 25 per cent monocytes and 3 per cent eosinophils. Stool cultures and smears showed the predominating organisms to be 99.9 per cent nonhemolytic *Bacillus coli acidilactici* and 0.1 per cent hemolytic streptococci. A catheterized urine specimen showed *Staphylococcus albus* and streptococci. Examination of the nose showed *Staph aureus* and an alpha *Streptococcus*. Cultures from the throat showed green streptococci, nonhemolytic streptococci, diphtheroids and gram-positive micrococci. Examination of the sputum showed green streptococci, streptococci with slight hemolysis, gram-positive micrococci and no hemolytic streptococci. The culture was not significant. Urinalysis gave normal values, and the Wassermann reaction was negative.

#### DISCUSSION

DR FRANK C COMBES I agree with the diagnosis.

DR R. H. RULISON I do not know what can be done in cases of this kind unless some obscure gastrointestinal disturbance is at fault. On an empiric basis I wonder whether colonic irrigations would have the effect of bringing down the sedimentation rate, which is the important thing in this case.

DR FRED WISE At least two articles have appeared in the past two years advising a trial of the sulfonamide compounds in cases of this kind. If there are no contraindications in this patient, I would be inclined to give them a trial.

DR A. BENSON CANNON I have had some remarkable cures by the use of iodine internally in several cases similar to that of the patient presented, and in only 1 of these was there what I thought was a slight recurrence of lesions one year after cure, though I have had patients under observation for as long as two years afterward. In the 1 recurrence there were only three or four pea-sized to dime-sized, erythematous lesions and these disappeared after use of iodine was resumed. My first patient was a woman with extensive lesions of the face, neck, ears, upper and lower extremities and chest with petechial hemorrhages and a slight elevation of temperature. She was admitted to the Presbyterian Hospital, where she was given 3 drops of 7 per cent tincture of iodine, increasing to 9 drops three times a day. She had clearing after two months and there was only a smooth atrophy of the skin. I painted one upper extremity with 7 per cent tincture of iodine twice a day, and the unpainted portions got well much faster than the one that had the iodine applied. Another patient, with a generalized lupus erythematosus of the subacute variety, I treated in the same hospital and in the same way, and he was discharged from the hospital five weeks later greatly improved. He resumed his occupation and continued his treatments at the office until cured. I also treated 3 other patients, 2 with less extensive lesions, and all successfully. I tried the same treatment on 3 patients with discoid lupus erythematosus who had failed to respond to other treatments over a period of years. Two of these patients were cured after a year's treatment, and the third was almost well when she disappeared from observation, only to return several months later with the condition just as extensive as before the beginning of treatment. Where the lesions have disappeared, the cosmetic result is much better than I have noticed with any other method of treatment, there being only atrophy and depigmentation remaining. When the patient has been unable to take iodine (because of an idiosyncrasy) I have given strong solution of iodine U. S. P. or sodium iodide intravenously, but it was my impression that they were not so beneficial as was the iodine.

DR FRANK C COMBES Is that treatment applicable to this type of lupus erythematosus? I have used it in treatment of the disseminate discoid type but never of the acute or subacute type. This woman has the latter, resembling, if not identical with, the Lillman-Sacks syndrome.

DR A. BENSON CANNON This is the particular type of case in which iodine is most effective. In 2 of our patients the eruption was so extensive, accompanied by hemorrhages and constitutional symptoms, as to cause us to fear a fatal termination. The encouraging results make me feel that a further trial with iodine in the treatment of lupus erythematosus is indicated.

DR EUGENE F. TRAHN Dr. Wise has recommended a trial of some of the sulfonamide compounds, but I wonder whether this would be advisable in view of the falling white blood cell count. I asked this because in a previous patient, under similar circumstances, sulfonamide drugs seemed to hasten a fatal termination. The use of small doses of gold or bismuth has been suggested and I believe that this might be safely tried, especially if we can get the patient in better physical condition. I have had a number of these patients whose lesions clear and who, so far as I have been able to follow, remain well simply with rest in bed and improvement of the general physical condition. It is therefore difficult to evaluate therapeutic results of any specific drug used during such a rest period. Recent tabulation from the Mayo Clinic indicates that persons with acute lupus are usually dead within a six month period, while those with subacute disseminated forms have a better prognosis with a fair percentage of recovery. Those patients who do not die usually survive for a longer period, even up to four and one-half years. While they used a variety of treatments, rest in bed and small transfusions apparently played an important role. The iodine treatment recommended by Dr. Cannon is entirely new to me, and I will be glad to give it a trial in this case and let the members know the result.

#### Rosacea-like Tuberculid (Lewandowsky) Presented by DR A. BENSON CANNON

Mrs. I. K., a widow aged 48, does her own housework. She has never been pregnant. The past history and family history are irrelevant. There is no history of tuberculosis in the family. The present eruption began two years ago, on the upper part of the sternum, as a red, burning, hot, itching papular rash that gradually crept up over the cheeks, nose, forehead and back of each ear. The lesions began as angry, red, small papules that felt sore to the touch. The eruption has never entirely disappeared. It has been treated by several dermatologists with lotions, salves and roentgen and ultraviolet irradiation, all without any improvement. She has been advised to have her tonsils removed, but her family physician said that she was too old to have this done. She has had patch tests for various cosmetics, all of which elicited negative reactions, but she discontinued the use of all these, including soap, without any improvement in the eruption.

The patient was treated at a local hospital from Dec. 3, 1942 to Jan. 12, 1943 for a dermatitis. Biopsy was performed, and the eruption was reported as being a tuberculid. Tests with old tuberculin in dilutions of 1 to 1,000,000 and 1 to 100,000 elicited negative reactions, and in a dilution of 1 to 10,000 a moderately positive reaction. A roentgenogram of the chest on March 25, 1943 showed a moderate degree of thickening at the hilus together with moderate generalized



pulmonary hypervascularization. There was no evidence of parenchymatous infiltration or of pleural thickening. The patient stated that the eruption on her face improved after she had the tuberculin tests.

Examination shows a well developed, apparently healthy woman of somewhat over middle age and a bit obese. General physical and neurologic examinations have revealed nothing significant except large and cryptic tonsils. Scattered over the face, especially on the cheeks, chin, nose and forehead and between the eyebrows, is a pinhead to millet seed sized, slightly grayish to erythematous, papular eruption. The lesions are discrete except for a few that have coalesced to a split pea-sized, slightly raised and scaly lesion of a slightly tan color. There is redness of the nose and cheeks, but there are no dilated blood vessels and no scarring. On pressure most of the lesions show a slightly tan, so-called apple jelly color.

#### DISCUSSION

DR FRANK C COMBES: How often does one see the hypoergy to tuberculin encountered in this case? Some investigators say these patients are hypoergic, but most of those that are seen are hyperergic, with a positive reaction to a 1 to 1,000,000 dilution or weaker of tuberculin.

DR FRED WISE: There appears to be a great variation in the responses to tuberculin tests. I do not think the tuberculin test is of any special significance in diagnosis, as the degree of hyperergy or hypoergy varies so much in this variety of cutaneous tuberculosis.

DR A BENSON CANNON: My experience has been similar to that of Dr Wise. I feel as he does about the tuberculin reaction in these cases, and I am not sure that they all fit clinically or histologically into the same general pattern described by Lewandowsky. Some patients having lesions that are most typical of rosacea-like tuberculid have negative reactions to tuberculin, while others with lesions that are equally characteristic of the disease have strongly positive reactions. However, in the two groups the histologic observations are the same. It is possible that this variation in the reaction of such patients to tuberculin can be explained by the fact that one group has a tuberculid while the other has true tuberculosis. While the disease is usually thought of as a tuberculid, Wile and Garver expressed the belief that the rosacea-like tuberculid of Lewandowsky is a true tuberculosis of the skin.

#### Lupus Vulgaris Presented by DR FRED WISE

A S., a woman aged 70, referred by Dr Charles Kimm Good, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Jan 12, 1944, presenting lesions of twenty years' duration. She is married, but she never conceived. Her family history is noncontributory. She gives no history of previous diseases of the skin. Her general health has been unaffected. She was treated with localized and generalized ultraviolet therapy for about six years. The response was only moderate. The lesions get worse in winter. There is slight itching but no pain.

The eruption began with a small "pimple" on the left ala nasi. It spread slowly up the tip of the nose and the right ala nasi in a contiguous manner within a period of three years. These lesions never healed. Two years ago both cheeks and the upper lip became involved. Six months ago the rest of the nose became affected and two months ago lesions appeared on the

There is a symmetric involvement of the entire nose, upper lip and the peripheral half of the cheeks. There is extensive destruction of the tip of the nose and the alae nasi. There are ill defined pea-sized and larger nodules, some discrete, most of them grouped, on an inflammatory base. They are raised above the surface and covered with a thick greenish yellow crust. There are healed areas with scarring. Most of the active lesions are at the periphery. Some of the lesions discharge a serous and bloody exudate. There are no lesions in the oral mucosa. There is a quarter-sized lesion in the middle of the inner side of the right leg which is infected. There are also scattered yellowish ill defined pea-sized to cherry-sized growths on the anterior surface of the left leg. On compression with a diascopic glass, some growths on the face reveal yellowish jelly-like nodules while those on the legs disclose yellowish stains.

The results of routine laboratory tests were normal. A section removed was examined histologically by Dr Charles F Simms. He diagnosed the eruption as lupus vulgaris.

#### DISCUSSION

DR EUGENE F TRAUB: It seems that the forms of cutaneous tuberculosis which one sees from time to time are subject to change with improved sanitation, living conditions and medical care of tuberculosis in general. Might this not account for some of the things looked on now as exceptional? This happens to be an Italian patient, and I wonder if it is just coincidence that many of the patients seen in New York with this destructive condition about the nose and face are members of that nationality.

DR FRED WISE: I do not know about that, but in Copenhagen there are hundreds of persons with lesions of this type.

DR PAUL E BECHET: I believe that Dr Wise presented this case because of the late onset of this dermatosis. I presented many years ago a case at either this society or the Manhattan Dermatologic Society of a man who had acquired lupus vulgaris at the age of 60. Since then it seems to me that the incidence of lupus vulgaris in the elderly has increased and a perusal of the literature and my own experience confirm the supposition.

#### Pigmentation of the Eyelids from the Use of Mercurial Ointment Presented by DR FRED WISE

Miss M R., aged 37, in excellent general health, had blepharitis ten years ago and was advised to apply yellow mercuric oxide ointment. Despite the fact that the blepharitis got well, she formed the habit of using the mercurial ointment daily and has been applying it for the past ten years. Other medicaments or cosmetics have never been applied to the eyelids or lashes.

The upper and lower eyelids show a conspicuous dark brown pigmentation, having the appearance of a dark cosmetic preparation that has been painted on. No other pigmented spots are noted in other regions.

#### DISCUSSION

DR EUGENE F TRAUB: This patient interested me particularly because some years ago I testified for a woman who had used Geraud's Oriental Cream for twenty-five years on her face and neck and had then acquired a pigmentation from the mercury as well as a systemic mercurial poisoning. Geraud's Oriental Cream was alleged to consist of 33.3 per cent mild



mercurous chloride in water, and because the base was water the contention was that the mercury would not be absorbed. While preparations in an aqueous vehicle are probably not absorbed so readily as others, certainly after such long-continued use there can be no question of the absorption, and the discoloration of the skin in all these cases, like the one just presented, is identical. Probably if use of the preparation is discontinued the skin will become lighter but I doubt that the color will return entirely to normal.

DR J GARDNER HOPKINS Does Dr Wise believe the pigment in this case to be a deposit of mercury in the skin, or is it an accumulation of melanin?

DR FRED WISE I do not know which it is. I should like to be able to answer Dr Hopkins' question. I have an impression that the discoloration is due to a deposit of particles of mercury rather than melanin. I have two books from Argentina, where the natives use a great many preparations containing mercury in cosmetics, in which many similar cases are described.

DR GEORGE C ANDREWS The name "Oriental Cream" has been on my tongue ever since the presentation of this case. I had a patient with this type of pigmentation in the nasolabial folds from the use of this cream.

#### Verruca Plana (Annular) Presented by DR GEORGE M LEWIS

K E, a young woman aged 18, a college student, first acquired small warts four years ago. Several months ago she was given a prescription containing tincture of cantharides in collodion. The application of this preparation caused blisters to develop. When the reaction subsided, the warts appeared at the periphery of the inflammatory zone.

The examination shows both solitary and grouped, flat warts, the latter showing a circinate arrangement. The lesions are present on both forearms and hands.

#### DISCUSSION

DR J GARDNER HOPKINS I had 1 case in which exactly the same thing occurred much to my dismay, but I do not know why. It had usually been my practice to take the wart off as soon as blistering occurred, and in that case the patient did not return in time. I presume that the wart virus spread to the periphery of the blister.

DR FRANK C COMBES How long after the cantharides blister was raised did these new lesions appear? As for treatment, I think the best is with solid carbon dioxide without forming a blister. Just a few seconds of exposure is all that is necessary to cause exfoliation of the warts.

DR FRED WISE I wonder whether Dr Lewis can be induced to obtain a specimen for biopsy from one of those lesions and report on it at the next meeting.

DR GEORGE M LEWIS I think that Dr Hopkins' explanation is the logical one, that the virus spread and formed new lesions at the periphery. I do not know of any other explanation that there could be for the dissemination, because in each lesion there was a spread beyond the original wart. In answer to Dr Combes's question, the lesions appeared a few days after the blistering.

#### Sarcoidosis Presented by DR A BENSON CANNON

D C, a West Indian Negro aged 43, single, is presented from the Vanderbilt Clinic where he was first

seen on Nov 10, 1943, complaining of elevated tender, painful lesions on the hands for three months and on the face for the previous six weeks. The patient states that he was well until six months ago, when pain and swelling of the wrists and hands developed. Similar pain and swelling appeared in the knees, ankles and feet. He visited a private physician, who gave him intramuscular and intravenous injections for "arthritis." He had tenderness of the fingers so that he could hardly pick up anything. Later the swelling of the joints and tenderness of the fingers subsided, but the fingers have been numb since then.

About three months ago tender, painful elevated lesions appeared on the hands. Also, asymptomatic elevated lesions appeared on the penis. The lesions on the hands caused a burning sensation day and night. About six weeks ago a lesion appeared on the upper lip and the nose. This was associated with a burning sensation and swelling. These areas are now slightly numb.

There is no history of any family diseases. The patient has not been outside the United States since he came here, nineteen years ago, from the British West Indies. He has worked as a waiter in one place for fifteen years. He has no knowledge of ever having had any venereal disease by name or symptoms, and the Wassermann reactions of the blood have always been negative. He has never received any antisyphilitic treatment. The only illness he can remember was pneumonia more than fifteen years ago.

The lesion on the nose involves all of it from between the eyebrows on both sides to and including the external nares, widening the alae and giving him a lion-like countenance. The lesion also involves the upper lip. It is erythematous, sharply demarcated and indurated, with some increased pigmentation of the borders. It is not tender to palpation. The surface is dry and is covered with a branny desquamation. There is no definite nasal discharge or crusting. The upper lip is swollen and indurated. No oral lesions are seen there is no alopecia of the eyebrows present and no nodules on the lobes of the ears can be found. The posterior auricular nerves are not palpable, and no posterior cervical nodes can be felt. The remainder of the face is clear. The anterior surface of the trunk is also clear. An oval, elevated, crusted, sharply demarcated lesion, measuring 2 by 3 cm, is present in the left lumbar area. A lesion similar in size and shape is present on the upper anterior part of the left thigh. The surface is glossy and appears to be composed of a compact group of flat papules measuring 2 to 4 mm in diameter.

Over the dorsa of the hands and fingers of both hands are discrete to confluent, elevated groups of glossy lesions that are of the same color as the patient's normal skin and appear nodular in some areas. The lesions are round to oval and 1 to 5 cm in diameter. Several are desquamating. Sharply demarcated, pigmented, infiltrated, painless lesions from 2 to 3 cm in diameter are scattered irregularly over the volar surfaces of the fingers and palms. No characteristic claw hand is present, and there is no atrophy of the interosseous muscles. There are similar but smaller, elevated, scaly, indurated lesions on the dorsa of the feet. Over the scrotum are numerous dry flat, slightly elevated, indurated discrete annular nodules, and irregularly over the shaft and prepuce of the penis are depigmented indurated areas. There is no evidence of a primary syphilitic lesion. No anal lesions are present. The inguinal and epitrochlear nodes are not palpable. The

ulnar nerves are palpable in both epitrochlear areas, but they are not nodular. All elevated lesions are anesthetic to touches of wisps of cotton.

The Kline test of the blood was negative. No acid-fast organisms were found in nasal smears. The stools were negative for ova and parasites. The urine was normal. The blood count showed 11 Gm of hemoglobin, 4,890,000 erythrocytes and 9,750 leukocytes, with a differential count of 48 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes, 13 per cent monocytes and 1 per cent eosinophils. Tests with old tuberculin elicited negative reactions in forty-eight hours with a dilution of 1 to 1,000,000 and a positive (1 plus) reaction in forty-eight hours with a dilution of 1 to 100,000. Roentgenograms of the hands showed demineralization of all the bones but no evidence of sarcoidal changes. A roentgenogram of the chest showed no evidence of enlarged hilar nodes and nothing to suggest Boeck's sarcoid. Examination of biopsy specimens taken from the dorsum of the right hand and the right nasolabial fold showed sarcoid of the skin.

#### DISCUSSION

DR J GARDNER HOPKINS. The differential diagnosis between sarcoid and leprosy is not easy to make histologically. There is much in this case to suggest leprosy.

DR FRED WISE. I do not think that I can offer any comments which are more to the point than what Dr Hopkins has said, but I know that the experts in leprosy lay great stress on the tests for heat and cold sensation in differentiating leprosy from other diseases. I presume the neurologist in this case made this test, but if it is not expertly and properly done it is not of much value. I should think that it would be one of the most important tests, if not the most important one, to be made in this instance. Furthermore, if this patient does not have any cystic lesions of the bones, I should be inclined to exclude sarcoid but not tuberculoid leprosy. In cases like this it is very difficult to discover the lepra bacillus either in the nasal smears or in the lesions themselves. I should be much more inclined on the basis of this examination to regard this as a case of leprosy than a case of sarcoid.

DR FRANK C COMBES. If this is not a case of neuroleprosy, it is an exact clinical counterpart with Jadassohn's sarcoid manifestation, more correctly called tuberculoid leprosy. I agree with Dr Wise. Of course there are many tests which should be made and a more detailed clinical examination should be performed by one acquainted with leprosy. One test which would be of great value is the histamine test to determine the integrity of the peripheral neurons. Incidentally, this patient gives a history of epistaxis and shows some pallor of the soft palate and pharynx.

DR WILLIAM CURTH (by invitation). I suggest that large doses of potassium iodide be given to this man to see if a good nasal smear can be obtained.

DR LEWIS B ROBINSON (by invitation). I think that this is one of the many manifestations of sarcoid in a Negro. Sarcoid does all sorts of queer things in Negroes.

DR JEROME KINGSBURY. No one wants to make a definite diagnosis in a complicated case with involved history from a single inspection. It is my impression, however, that the case is one of maculoanesthetic leprosy which is perhaps about to turn into the mixed type. There are enlargement of the ulnar nerves and atrophy of the muscles of the hands.

DR A BENSON CANNON. I am pleased to have your opinion of the diagnosis for this patient. I was unable to rule out leprosy clinically, although we could not find the bacilli. This patient's having come from a part of the world where leprosy is prevalent, the locations and character of the lesions, the enlargement of the ulnar nerves, the atrophy of the interdigital muscles, the defective sensation to touch and the absence of osseous changes on roentgen examination caused me to make a diagnosis of leprosy. However, this diagnosis had to be discarded because we could not find the bacilli in secretions taken from the nose or in stained sections. We have had several persons with manifestations similar to this one in the clinic during the last few years, and, while they have all had symptoms strikingly like those found in leprosy, we have been forced to make our final diagnosis sarcoid because of the failure to prove leprosy.

DR FRED WISE. Are there any reports of atrophy of the interosseous muscles of the hands occurring in sarcoid of nonleprous origin?

DR WILLIAM CURTH (by invitation). We have a report from the members of our medical department stating that this atrophy can be due to disuse. The bones of the fingers show demineralization due to disuse also.

DR EUGENE F TRAUB. I have heard this man's eruption described by some as maculoanesthetic leprosy and by others as sarcoidosis. Is not sarcoidosis a nodular eruption? How can the eruption be macular and nodular at the same time?

DR A BENSON CANNON. The lesions have been nodular at all times, although the periphery of the affected parts has flattened appreciably in recent weeks.

#### Granuloma Annulare (Generalized) Presented by DR GEORGE C ANDREWS

Mrs J J, aged 60, six years ago first noted the development of ringlike lesions on the sides of the neck and wrists. These were treated with roentgen rays. She thinks that she has had about eight treatments to her neck and the upper part of her chest. The eruption disappeared, and then it recurred six months ago, beginning on the wrists and spreading to the shoulders and thighs.

Examination shows a generalized eruption which involves mostly the shoulders, chest, wrists and thighs. The infraclavicular regions are covered with curved, linear and annular lesions that form spiral patterns. On the anterior aspects of the wrists and on the inner sides of the thighs, there are annular lesions and incomplete rings. On close inspection, the lesions are elevated and are made up of small deep-seated papules and nodules. The overlying epidermis is apparently normal except on the sides of the neck, where there is a suggestion of atrophy that is possibly due to the roentgen ray treatments.

Results of urinalysis were negative for sugar and albumin and normal in other respects. The Wassermann and Kahn reactions were negative. Biopsy of an annular lesion on the tip of the right shoulder showed the epidermis relatively thin and somewhat edematous. There was a diffuse infiltration of the cutis, with focal granulomatous changes. About the foci of degeneration there were infiltrations of epithelioid cells and an occasional giant cell was seen. There was also diffuse and focal infiltrations of what appeared to be lymphocytes. The changes were those of granuloma annulare.

## DISCUSSION

DR J GARDNER HOPKINS If this is granuloma annulare, it is an extraordinary type. If it is a tuberculoïd syphilid, it is a rather common type. On hasty examination of the slide I could not make the diagnosis of granuloma annulare. My clinical impression was that this is a syphilid.

DR PAUL E BECHET On clinical grounds alone this woman has a typical and classic granuloma annulare on the wrist, and the lesions on the upper part of the chest also seem to me to present fairly conclusive evidence of granuloma annulare. Dr Andrews raised the question whether the atrophy on the neck may have been due to roentgen therapy. I believe not. I think it is simply the atrophy resulting from healing of the lesions of granuloma annulare. I agree entirely with the diagnosis of granuloma annulare.

DR FRED WISE I agree with Dr Bechet.

DR JOHN C GRAHAM My impression is that this is granuloma annulare rather than syphilis.



Fig 1—Granuloma annulare (generalized)

DR FRANK C COMBES I think that it is granuloma annulare, but I want to ask a question. In some cases of granuloma annulare there is prompt response to roentgen rays, but in others the disease has impressed me as being very resistant to roentgen irradiation. Is that your experience?

DR EUGENE F TRAUB To answer Dr Combes's question, lesions of granuloma annulare vary in their response to roentgen rays just as the tuberculin reactions vary.

DR GEORGE M LEWIS This is a striking and unusual case. Many of the lesions are typical of granuloma annulare, but I think that it is most unusual to see the symmetry and the continuous lesion which this woman presents across the back.

DR GEORGE C ANDREWS Dr Machacek made the histologic examination. He said that there were no changes in the blood vessels indicative of syphilis. The Wassermann and Kahn reactions are both negative. The eruption has improved in the past week. The patient has had two roentgen ray treatments and two

intramuscular injections of a bismuth preparation, which I gave her on the basis of treating lichen planus. I thought at first that the eruption was either granuloma annulare or lichen planus, because there were well defined papules which were a little lichenoid and the distribution of the eruption was suggestive of lichen planus, beginning on the flexor surface of the wrist and the inner side of the thigh and spreading over on the neck.

### Dermatitis Medicamentosa et Venenata (Sulfathiazole)

Presented by DR GEORGE M LEWIS

M R, a man aged 41, is presented from the New York Hospital. He first had a rash on the mucous membrane of the lips eight months ago, for which he sought aid at various clinics. Four months ago, on the advice of a physician, he applied a liquid preparation for several weeks. Some of the preparation touched the skin of the upper lip, and a rash then began which quickly spread over the face, accelerated, the patient thinks, by his use on the new areas of the same liquid preparation. When he stopped its use and applied wet compresses of solution of boric acid, the rash quickly disappeared. He then applied sulfathiazole cream to his lips, and eighteen to twenty hours after this one application a similar spreading dermatitis appeared on the face. When he used boric acid compresses the eruption disappeared. Three days ago, after the extraction of two teeth, his dentist gave him pills, directing him to take 4 pills immediately and 2 pills every four hours. He took 8 pills altogether, and in about twenty-four hours from the time he took the first ones an exudative and edematous, extremely pruritic eruption appeared on the face in approximately the same areas involved in the first two attacks. So far as he can tell, the present rash is more severe than but otherwise not different from the previous attacks. At present there is a resolving dermatitis of the face, ears and anterior portion of the neck. No other parts of the body are affected. The pills were found to be sulfathiazole (0.5 Gm).

## DISCUSSION

DR EUGENE F TRAUB I agree with the diagnosis as presented.

DR J GARDNER HOPKINS This is a beautiful example of the phenomenon, emphasized first, I think, by Jadassohn, that identical reactions to sensitization occur whether the allergen is applied externally or internally. The reaction from without and the reaction from within are of the same character.

DR R H RULISON Does the reverse happen? If one takes sulfathiazole internally and later uses it on the skin, is there any sensitization?

DR FRANK C COMBES No. The reverse reaction does not occur.

DR PAUL E BECHET In reference to the question of induced sensitization from the local use of sulfathiazole ointment, I wish to state that I gave 10 per cent sulfathiazole in an oxycholesterol-petrolatum base (Aquaphor) to a patient with two or three small furuncles in his left nostril. After its application for two or three days the patient was so well that its use was discontinued. There was no reaction from the ointment. Some time later, a new boil developed on the patient's arm, to which he applied the same ointment used in his nose. Within forty-eight hours a severe vesicular dermatitis developed on the boil and its adjacent area which lasted for several weeks. A strongly positive reaction to a patch test on normal skin

with the same ointment confirmed the sensitization. Apparently the infinitesimal amount used in the nostril had caused the sensitization.

DR GEORGE M LEWIS Because of the possibilities of initiating sensitivity, patch tests with the sulfonamide compounds should not be carried out routinely.

#### Familial Benign Chronic Pemphigus Presented by DR J GARDNER HOPKINS

A D, a married woman aged 41, a Puerto Rican, has had typical lesions of familial benign chronic pemphigus for about sixteen years. The lesions occur on various areas of the body, mostly around the neck, under the breasts and on the arms and hands.

The patient's mother had this disease of the skin. It cleared after her menopause, and she is now completely well. The patient had two brothers who are affected, one is well and healthy but always has some eruption, while the other brother had this disease and died in Puerto Rico of an anemia. The patient has three children. One child, aged 4, has eczema, another has occasional herpes labialis. The patient's general health is good except for the cutaneous disease.

Histologic examination of a biopsy specimen was made by Dr G F Machacek and was reported as familial benign chronic pemphigus (Hailey-Hailey type).

The case is presented for therapeutic suggestions. The patient has been treated with snake venom, vitamin K, injections of liver and arsenicals, with temporary remission but no cure.

Examination at the present time shows in the inframammary folds and on the upper part of the abdomen dusky erythematous plaques with some ruptured bullae at the borders. There are also some dry scaling plaques on the back of the neck.

#### DISCUSSION

DR FRED WISE I agree with the diagnosis. I cannot offer any suggestions as to therapy in addition to amelioration with roentgen rays.

DR EUGENE F TRAUB As Dr Wise has suggested, I also recommend treatment with roentgen rays.

DR LEWIS B ROBINSON (by invitation) The interesting feature is that this woman's mother had this disease and it cleared after she reached the menopause. She is now about 70 years old, and has not had any lesions since the time of her menopause.

#### Mycosis Fungoides Reported by DR FRED WISE

H G, a man aged 78, was presented before the New York Dermatological Society on Dec 21, 1943.

#### DISCUSSION

DR EUGENE F TRAUB The diagnosis in this case was determined by microscopic examination, I believe, but the patient also had a 4 plus Wassermann reaction. As I raised the question at the time of presentation as to whether tertiary syphilis had been ruled out, is Dr Wise able to tell us at this time the outcome in this case?

DR FRED WISE We do not know yet what the diagnosis is. The clinical appearance a week after presentation was that of tertiary syphilis. Jessner and Sims both thought it was mycosis fungoides because of results of biopsy. I believe with Dr Traub that the patient has syphilis and not mycosis fungoides. Still the histologic observations are indeterminate, and further studies will be required.

## CHICAGO DERMATOLOGICAL SOCIETY

MICHAEL H EBERT, M D, *President*

MARCUS R CARO, M D, *Secretary*

*Dec 15, 1943*

#### Lupus Erythematosus Disseminatus Subacutus Presented by DR M H EBERT and (by invitation) DR M OTSUKA

M C, a white woman aged 35, presents an eruption on the face, neck, chest, arms and hands. The first lesions appeared on the V of chest and the radial portion of each forearm in May 1943 after a sunburn. The lesions were itchy, they soon spread to the face. She has felt fairly well otherwise. Her appetite is good, she has lost no weight. Her fingers feel stiff when she awakens in the morning.

She is married and has two children, aged 14 and 16 respectively. There have been no miscarriages. There is no history of tuberculosis in her family.

She has been under observation for four weeks. When first seen there was an almond-sized tender lymph node palpable at the exterior margin of the right pectoralis muscle. The axillary and epitrochlear nodes were enlarged. The spleen was enlarged.

The vitamin A level of the blood was half the normal value, but the carotene level was normal. The urine was normal on two occasions. On her admission to the hospital on November 18, examination of the blood showed 3,500 leukocytes, 82 per cent hemoglobin and 4,080,000 erythrocytes. After one blood transfusion the leukocytes went up to 4,100 on December 2. The ascorbic acid level was decreased to 0.3 (normal 0.7 to 1.4) mg per hundred cubic centimeters. The non-protein nitrogen and blood sugar levels were normal. The albumin-globulin ratio was reversed. The Wassermann reaction was negative. The electrocardiogram was abnormal, but the cardiologist could not identify the lesion. On auscultation there were no abnormal sounds. The roentgenograms of the heart and the pulmonary fields were normal.

The skin of the face is bright red and slightly infiltrated, with sharply defined margins. There are similar changes on the V of chest and neck, but the skin is more mottled with slight atrophy. There are no lesions on the chin and the center of the forehead. The lips and mucous membranes are normal. The radial surfaces of the forearms are similarly marked. The lesions on the back of the hands have undergone partial involution. Her hair is scanty, and she has an area of erythema in the vertex that comes and goes. There is some residual scaling on the arms. Her temperature is usually up to 99 but at times to 101 F.

The epidermis was atrophic. There was a moderate hyperkeratosis. The papillae were flattened, and the rete was reduced in places to three rows of cells. There was edema of the rete mucosa, and in places there was liquefaction necrosis of the basal layer. The sub-papillary layer of the corium was edematous and infiltrated with many round cells. The capillaries and lymph spaces were dilated. The elastica was partially destroyed in this area.

#### DISCUSSION

DR S ROTHMAN (by invitation) It is interesting to note that the lesions are restricted to the exposed parts, with a rather sharp borderline. The patient volunteered the statement that the lesions developed after intense exposure to the sun. In 1 of my patients

with subacute disseminated lupus erythematosus, I found that ointments containing paraaminobenzoic acid gave complete protection against the provocative effect of sunshine. From this observation one may conclude that the provocative effect of sunshine in lupus erythematosus is due to the so-called "sunburn rays" or "erythema rays" in the region of 3,000 angstroms because paraaminobenzoic acid filters off only these rays.

DR HAMILTON MONTGOMERY, Rochester, Minn. At the Mayo Clinic we have so far failed to obtain beneficial results from the use of penicillin in the treatment of lupus erythematosus.

DR M H EBERT. One interesting thing about this case was the character of the enlargement of the lymph nodes which is frequently present in persons with the disease and was in this patient. She had one rather large node under the pectoral muscle when we saw her a month ago, but it has now receded. She still has some adenopathy in the axillary folds. This lymphatic enlargement in acute, and subacute lupus erythematosus is frequently present.

Another thing is that about five days ago she had a rather acute upset with fever. Her temperature was high and she felt sick. I do not believe that it was due to the epidemic of disease of the upper respiratory tract which seems to be present throughout the country. She had no respiratory symptoms. She was given two more blood transfusions and rapidly improved. I wonder how accurate I am in calling this woman's disease subacute. She continues to have a little elevation of temperature, 99 and sometimes 100 F. Perhaps that should be classified as acute lupus erythematosus.

DR S ROTHMAN (by invitation). A lesion on the forearm shows definite atrophy, and therefore I believe the case should be classified as an instance of subacute disseminated rather than acute lupus erythematosus. In the lesions of the acute form one never sees atrophy developing.

#### A Case for Diagnosis (Sarcoid?) Presented by DR A W STILLIANS

A housewife of Norwegian birth, aged 37, entered the City of Chicago Municipal Tuberculosis Sanitarium in January 1938, with a history of progressive loss of weight, dyspnea and persistent cough. A diagnosis of pulmonary tuberculosis had been made and was confirmed by physical examination, roentgen ray examination and repeated cultivation of tubercle bacilli from the sputum. On entrance she had a scaly patch in the scalp near the vertex and another, not scaly, on the right side of the forehead, partly within the hair line. Both were violaceous red and were neither sensitive nor causing any discomfort. A biopsy from the lesion near the vertex showed a few groups of epithelioid and round cells with a few small giant cells. The lesion on the vertex was about 2 by 4 cm and the one on the forehead slightly larger. Neither showed any palpable infiltrate.

Her blood at this time was normal, about 70 per cent hemoglobin and a leukocyte count of about 4,500, with the different varieties in the usual proportions. The tuberculin tests elicited negative reactions. With mild treatment, consisting of application of ammoniated mercury ointment and of another ointment containing 5 per cent resorcinol, the lesions cleared, first becoming brown and then fading entirely.

In April 1941 she had a recurrence of the eruption, which when seen in October of the same year presented a polycyclic patch 2.8 by 2 cm above the external end

of the right eyebrow and two very small macules at the hair line in the center of the forehead. Partly within the hair line on the left side of the forehead was a macule 2 cm in diameter. None showed any elevation above the level of the skin or any palpable infiltration, they were sharply defined with smooth borders and a pale slightly brownish red. The blood at this time contained 4,980,000 red blood cells, 80 per cent hemoglobin and 4,300 leukocytes. The sedimentation time was within normal limits. This eruption cleared slowly with administration of ammoniated mercury ointment.

When seen a week ago there was a macule 4 cm in diameter on the right side of the forehead within the hair line. A second macule, 9 mm in diameter, was situated just below the hair line at the center of the forehead and the third, 2 cm in diameter, on the left side within the hair line. They were all violaceous dull red, the larger one being slightly brownish red. On the nape of the neck within the hair line and slightly below it, there is a slightly keratotic patch which itches at times. It does not resemble the others.

#### DISCUSSION

DR S W BLACK. This annular lesion is similar to one I presented a year or two ago, with the peripheral linear elevation and the atrophic center. Sarcoid is not supposed to produce this destruction. In the patient there was definite atrophy in the center of the lesion. The microscopic section would, I think, warrant a diagnosis of sarcoid.

DR C W FINNERUD. If the sections bear out the diagnosis of sarcoid, I believe that this diagnosis of annular sarcoid is correct. I could not find the sections.

DR M H EBERT. I think that Dr Finnerud will recall a patient of Dr Ormsby's, who is pictured in the latest edition of the textbook, with annular sarcoid of the forehead in the same area. His case was a duplicate of that of the patient shown today. As I recall there was little atrophy in that case, which was resistant to treatment.

DR HARRY R FORSTER, Milwaukee. Dr Stillians presented two slides, one compatible with a diagnosis of lupus erythematosus and the other one favoring sarcoid. It was my impression that the slide from the patient with the lesion on the forehead was one that presented a picture of lupus erythematosus. Is that correct?

DR A W STILLIANS. That is correct.

DR HARRY R FORSTER, Milwaukee. My thought was that the lesions could be either erythema perstans or lupus erythematosus, though they were not typical of either disease. They were not characteristic of the telangiectatic type of lupus erythematosus, and there were no follicular plugs or atrophy.

As regards a diagnosis of erythema perstans, the lesions were not pigmented, and though they were said to have varied in color and in size from time to time they never have been bright red, as is usual in lesions due to medication. While the patient was in the tuberculosis sanatorium when the lesions appeared, no medication was received. I favor a diagnosis of atypical lupus erythematosus.

DR A W STILLIANS. My personal opinion when she had the lesion on the scalp was that it was lupus erythematosus. That cleared without atrophy.

In regard to sarcoid, I doubted it because of the lack of infiltration. Dr Sweany, the pathologist at the Municipal Tuberculosis Sanitarium, is strongly in favor of a diagnosis of sarcoid. That is borne out by the



pulmonary changes, which were not those of an active tuberculosis. There were extensive fibrotic changes.

DR M H EBERT Do you recall, Dr Stillians, whether tubercle bacilli were ever demonstrated in this case?

DR A W STILLIANS They were found on animal inoculation after a number of efforts. It was difficult to demonstrate them.

#### A Case for Diagnosis (Lupus Erythematosus?).

Presented by DR M H EBERT and (by invitation)  
DR M OTSUKA

V A, a white woman aged 25, presents an eruption on the extremities. The first lesions appeared on the forearm one year ago. No new ones have appeared in the past three months. There is no subjective complaint. The patient is married and has one child. She appears strong and healthy. There is no history of medication.

There was nothing significant in the hematologic examination. The Kahn reaction of the blood serum was negative. The blood chemistry was normal.

The cutaneous lesions are relatively few. They are symmetrically disposed on the upper and lower extremities. There are three types of lesions. One type consists of a split pea-sized maculopapule with a central, white, adherent scale and a pinkish rim, the second type consists of a maculopapule 1 cm in diameter with a slightly scaly center and a depigmented periphery which is exaggerated by stretching the skin. On the palms there are a few match-head-sized flat-topped papules with a keratotic center and pinkish periphery. On the thighs and dorsa of the feet there are a few relics which appear slightly atrophic. There are no changes in the nails and no significant changes in the scalp or on the mucous membrane.

#### DISCUSSION

DR S ROTHMAN (by invitation) I did not see the sections, but the clinical picture certainly is compatible with the diagnosis of chronic lupus erythematosus. There is follicular plugging, and the lesions heal with a fine atrophic scar.

DR S W BECKER The sections could indicate either lichen planus or lupus erythematosus. When differentiation rests between the two, the diagnosis usually turns out to be lupus erythematosus. The woman did not seem to be as ill as a person would be with lupus erythematosus. Some of the lesions were in the typical location for lichen planus. I think that the diagnosis rests between the two diseases.

DR HAMILTON MONTGOMERY, Rochester, Minn. This case is similar to one which was presented by Dr O'Leary and Dr Goeckerman at the meeting of the Minnesota Dermatological Society on July 10, 1926 (ARCH DERMAT & SYPH 15 93-95 [Jan] 1927). Dr Ormsby, in the discussion of this case, remarked about the numerous lesions resembling lichen planus. Originally, this case was classified as one of disseminated lupus erythematosus. Since then my colleagues and I have had several patients with lesions resembling lichen planus, which we have come to regard as a generalized discoid type of lupus erythematosus because in all of them, including the first, there has been an absence of constitutional or systemic manifestations and because in all of them the disease has run a chronic, rather indolent course. The patient presented in 1926 when last heard from, a few years ago, was alive and well.

It is my belief that in the absence of leukopenia or any systemic manifestation this patient's case belongs in this group of cases of chronic generalized discoid lupus erythematosus simulating lichen planus but distinct from lichen planus and also that she should have a good prognosis.

DR M H EBERT We have observed this young woman for a considerable period. We are always puzzled about the diagnosis. When I first saw her I thought of lichen planus. Some of the lesions were annular, and I thought that the eruption might be atypical lichen planus. Another thought was that it might be syphilis, but the Wassermann test was repeated and the Kahn reaction was on different occasions in different laboratories, and all tests elicited negative reactions. This patient has some stigmas suggestive of congenital syphilis, but even if the disease were congenital syphilis it would not make this a syphilitic eruption.

Another thing I thought of was erythema nodosum, but the persistence of the lesions did not bear this out. We had two sets of sections, and I must confess that I did not appreciate the fact that this could be an atypical lupus erythematosus. I thought it might be a toxic eruption of the erythema perstans type. I am willing to accept the diagnosis of lupus erythematosus of the discoid type, but I must say that it is an extremely unusual one.

#### A Case for Diagnosis (Lupus Erythematosus?).

Presented by DR HERBERT RATTNER and DR. MAURICE DORNE

Mrs E F, a Negress aged 30, presents pigmented lesions on the face, arms and legs. The first lesions appeared on the extremities two years prior to presentation, the lesions on the face, six months later. They have persisted since the onset. The patient was admitted to the medical ward because of arthritis of the right wrist and edema of the forearms, both of one month's duration. There is a swelling of the left parotid area of one week's duration. There is a history of articular pains in childhood and also during the past three years. She had scarlet fever in 1931. She has been taking "a blood medicine" for the past three years.

There are sharply defined smooth flat hyperpigmented patches on the face and extremities, most of them of the size of a small coin. There is a small coin-sized reddened patch in the right buccal mucosa. Since her admission to the hospital the temperature has varied from 99 to 102 F and the right parotid area has become swollen, but there have been no new cutaneous lesions. The heart is normal, the spleen and the edge of the liver are not palpable. The lymph nodes of the cervical, axillary and inguinal areas are moderately enlarged.

The tuberculin test with a 1:10,000 dilution elicited a negative reaction. On Nov 6, 1943, the erythrocyte count was 3,730,000, the leukocyte count 8,150 and the differential count normal, and on November 30 there were 2,750,000 erythrocytes and 9,200 leukocytes. The sedimentation rate was 18 mm in twenty-five minutes. The Kahn reaction was negative. The agglutinations with typhoid H and O bacilli were negative, positive at 1:640 with paratyphoid A and negative with paratyphoid B. The chemical examination of the blood revealed calcium, 8.95 mg per hundred cubic centimeters, ascorbic acid, 0.5 mg, phosphorus, 2.5 mg, nonprotein nitrogen, 35 mg, total protein, 7.1 mg, albumin, 3.7 mg, and globulin, 3.4 mg.



The urinalysis showed normal values aside from a trace of urobilinogen. On one occasion *Streptococcus viridans* was recovered from a culture of the blood and *Bacillus coli* and *Staphylococcus albus* from a culture of catheterized urine. The results of stool culture were negative. The basal metabolic rate was -7 per cent, and the electrocardiogram gave a tracing of sinus tachycardia. Roentgenograms of the chest and of the hands were normal. A test dose with 1 grain (0.065 Gm) of phenolphthalein failed to excite the cutaneous lesions.

#### DISCUSSION

DR E. A. OLIVER: While there was not a great deal of evidence of lupus erythematosus on the skin, there was a definite patch of what apparently was lupus on the right buccal mucosa. I believe this is a case of lupus erythematosus.

DR M. H. EBERT: I saw the patient in the medical ward, just as Dr. Rattner did. The internist did not seem to have much idea about the diagnosis. She has arthritis and had had a low grade fever, and, I believe, the pigmented lesions on the body were considered an aftermath of the arthritis. I think, as Dr. Rattner does, that it is more apt to be lupus erythematosus, particularly because of the lesion on the buccal mucosa which Dr. Oliver mentioned.

DR HERBERT RATTNER: We favored the diagnosis of lupus erythematosus because of the lesion in the mouth, the generalized adenopathy, the low ascorbic acid level in the blood serum and the abnormal albumin-globulin ratio.

#### Lupus Vulgaris Improved by Internal Medication Presented by DR. A. W. STILLIANS

V. W., a Negro woman aged 25, entered the City of Chicago Municipal Tuberculosis Sanitarium in May 1943, complaining of progressive loss of weight, weakness, cough and dyspnea on exertion for about a year. She also had a swollen and tender right ankle.

The physical examination gave evidence of a quiescent pulmonary infiltrate.

The blood pressure was 120 systolic and 80 diastolic, and the hemoglobin content 70 per cent (Dare). The hematologic examination showed 4,560,000 erythrocytes and 5,200 leukocytes, of which 64 per cent were polymorphonuclears (stabs 7 per cent and segmented forms 57 per cent), 20 per cent small lymphocytes, 9 per cent large lymphocytes and 7 per cent monocytes. The sedimentation rate was 22 mm in thirty minutes. The Wassermann and Kahn reactions were negative. The Mantoux reaction to a 1:1,000 dilution of old tuberculin was 1 cm in diameter. Tubercle bacilli were not found in the sputum or in washings of the stomach on repeated tests. Inoculation of guinea pigs with sputum gave no infection (tuberculous).

The roentgen examination of the chest showed "pronounced infiltration downward on the right side extending into the base of the lung. It is apparently a mediastinal process and is most likely tuberculous." On examination of the throat, nodules but no papillomas were seen on the epiglottis.

When I first saw her, on May 26, she had several small papules, dark brown and soft, on both lower eyelids, the largest about 3 mm in diameter and projecting about 2 mm above the surface of the skin. On the upper rim of the left ear was a group of similar papules up to 5 mm in diameter and as elevated as the others. Another group of similar papules was located on the edge of the left nostril and still another on the upper

lip just below the nostril. On the external surface of the left forearm just distal to the elbow were several flat nodules 5 to 8 mm in diameter, darker brown than those on the face, soft and only slightly elevated. Under the dioscope a few apple jelly spots were visible.

Histologic examination of a section from one of these nodules showed a diffuse infiltrate of round cells in the dermis, angular cells with large pinkish protoplasm. In places these were arranged in loose groups. A tendency was shown to group as small giant cells. One typical Langhans giant cell was seen. In the older part of the process heavy bands of hyalinized connective tissue were seen, but no centers of caseation. No tubercle bacilli were found directly or on culture.

On June 23 treatment was begun with a sulfone drug related to promin (p,p'-diaminodiphenylsulfone-N, N'-dioxetose sulfonate). Soon after this cyanosis of moderate degree was noted, but the treatment was continued without other bad effect. Within a month a decided improvement was seen in the eruption, flattening and shrinking. The leukocyte count decreased slowly and after three months of treatment had reached 3,500, the erythrocytes numbering 3,000,000. The treatment was discontinued. By this time the papules on the eyelids had disappeared and the other lesions were much less conspicuous. At present the groups on the ear, nose and upper lip are composed of tiny papules 1 to 2 mm in diameter.

The left ear shows a congenital deformity consisting of three soft pedunculated projections like accessory lobes in front of the center of the external ear and two nodules with cartilage in closer to the auricle.

#### DISCUSSION

DR RUBEN NOMIAND, Iowa City: I believe that the differential diagnosis rests between sarcoid and lupus vulgaris, with the probability that it is sarcoid. The biopsy was not typical of sarcoid as it is seen in Negroes but I thought that the lesions that were shown and the location were typical of sarcoid. I believe that one should search further to see if other evidence of sarcoid can be found, particularly in the chest, and I think that better sections need to be made. If the diagnosis is doubtful, a tuberculin test would help and possibly even animal inoculation.

DR C. W. FINNFRUD: I think that those were the sections I saw. They were better sections of lupus vulgaris than they were of sarcoid, but with the history of lesions on the nose, eyelids and ears, I think the case falls into that group of cases of sarcoid that Dr. Nomiand described years ago. I should be in favor of another biopsy under the circumstances.

DR A. W. STILLIANS: The lesions have changed a great deal since treatment was begun. The point in favor of sarcoid is the negative tuberculin reaction, but the pulmonary condition is a typical tuberculosis. On three occasions cultures of the sputum were positive. I thought this was a case of lupus vulgaris because of the hypertrophic and nonulcerating lesions on the nose seen in Negroes. I thought that I found a few apple jelly spots.

#### Cervical Herpes Zoster Associated with Bell's Palsy Presented by DR. M. H. EBERT and (by invitation) DR. M. OTSUKA

A. B., a white woman aged 63, noticed an itchy and uncomfortable sensation on the right side of the nucha ten days ago. Later the area became painful. Two days later reddish nodules appeared. Five days ago she noticed a peculiar sensation back of the right ear,

and three days ago she awoke with palsy of the right side of the face. She experienced no dizziness, no tinnitus and no nausea. She had been well previous to the onset.

She has palsy of the right side of the face involving the forehead. It is impossible for her to close the right eye, and there is some lacrimation. On the right side of the nucha there are several small groups of match-head-sized bright red nodules. There is one group in the postauricular space and one inside the hair line. The lowest lesion is on the right clavicle. There are no lesions in the auditory canal or on the mucous membrane of the mouth.

#### DISCUSSION

DR S W BECKER Recently I read in one of the symposiums at the Chicago Medical Society that Bell's palsy is due to the virus of anterior poliomyelitis. I wonder whether this virus could produce herpes zoster.

LIEUTENANT A H SLEPYAN (MC), USNR I saw an 18 year old recruit who presented the picture of bilateral herpes zoster of the face, which came on one week after an attack of acute catarrhal fever. On the left side of the face, one group of lesions followed the maxillary branch of the facial nerve, another group appeared along the course of the mandibular branch. On the right side, the eruption appeared over the maxillary and postauricular branches, involving the upper pole of the ear. There were no associated symptoms.

DR HAMILTON MONTGOMERY, Rochester, Minn A few months ago I saw a case of herpes zoster associated with Bell's palsy. This combination is relatively rare.

DR S ROTHMAN (by invitation) I should like to ask for an anatomic explanation of this association. The fibers of the facial nerve do not pass through the spinal ganglion, which is the site of the pathologic process in zoster.

DR M H EBERT I do not presume that this case interested the other members as much as it did me. I have been particularly interested in herpes zoster, and some years ago I presented a case of a woman physician from the faculty of Rush Medical College who had Bell's palsy associated with zoster of the geniculate ganglion. This is the type which Ramsey Hunt associated with pain in the ear. Dermatologists do not see these patients because they go to the otologists. When the rash appears on the body the diagnosis is made of geniculate ganglion zoster. I hoped that was the diagnosis when I saw this patient the first time. On more careful examination I had to change my ideas. It is not uncommon for two levels of the cord to be involved in zoster, so it is clearly possible to have the second and third cervical associated with geniculate ganglion zoster but I do not believe this is a geniculate ganglion zoster. We had this woman examined by neurologists. They told us that it was too deep in the bony canal for involvement of facial sensation and two thirds of the tongue on that side. The face is normal, and they decided that the involvement was exterior to the bony canal, the type called Bell's palsy due to cold, virus infection and what not. The possibility that Bell's palsy is due to a virus, I cannot discuss. It is possible that the virus of zoster, just as the virus of poliomyelitis, is able to involve the facial nerve. On the other hand, it seemed to me that it began centrally. If it began centrally one would not have the present picture. If it began in the brain there would be paralysis of the sixth nerve involving the abducens nerve, which is not present. The neurologists are of the opinion that the

paralysis is exterior to the cranium. Examination of the ear was made, and the audiogram showed perception of high and low tones the same on both sides, hence there was no involvement of the auditory nerve either. I think this is a coincidental observation, and I cannot associate it with a zoster virus.

#### A Case for Diagnosis (Pemphigus Erythematosus?) Presented by DR S ROTHMAN (by invitation)

Z H, a white woman aged 48, married, was presented before this society on March 17, 1943, with the diagnosis of questionable pemphigus vulgaris. At that time she had a recent outbreak of large bullae on the trunk and extremities and a strongly positive Nikolsky sign. The circinate lesions with superficially eroded



Fig 1—Pemphigus erythematosus?

edges and with a tendency to serpiginous configuration, as seen today, had been present at that time for six months and have been present now for fifteen months. The majority of the members who discussed the case favored the diagnosis of pemphigus erythematosus. The possibility of pemphigus foliaceus was also mentioned (ARCH DERMAT & SYPH 48 469 [Oct] 1943).

Since the first presentation the patient has been hospitalized. New bullae appeared and healed in the following four months. After July 1943 no new bullae appeared. The whole surface of her body has been covered with the circinate figures with eroded edges, which at times show more tendency to spread and at times show good tendency to heal. Itching, at times exasperating, has always been present. The general condition has been fair throughout.

The last microscopic examination was made five days ago. Similar to the earlier ones the sections showed

subacute dermatitis with secondary infection and intercellular edema in the epidermis. The section is presented. Bacteriologic examination of the cutaneous lesions repeatedly yielded hemolytic *Staphylococcus aureus* and a few diphtheroids. The Wassermann and Kahn reactions were negative. The urine did not contain pathologic constituents throughout the whole course of observation. There has been a leukocytosis, the count varying between 9,000 and 18,000 white blood cells. In the beginning of the period of observation the percentage of polymorphonuclear leukocytes was above 80, of lymphocytes 16 and of eosinophils 2 to 3. Lately the polymorphonuclears dropped slightly, to around 70 per cent, and the percentage of lymphocytes increased correspondingly. The number of eosinophils rose at times to 7 per cent. Detailed studies of blood chemistry did not reveal abnormal values.

Acetarsone (total dose 182 tablets of 0.25 Gm each), sulfapyridine, sodium thiosulfate, calcium gluconate, ultraviolet irradiation and external applications of different kinds did not influence the course or the itching noticeably. However, the permanent disappearance of bullae coincided with the administration of large doses of acetarsone. Lately, the patient has tolerated ammonia mercury ointments, and they seem to have some beneficial effect. Sulfur-containing ointments are not tolerated. Prolonged potassium permanganate baths have a subjectively favorable effect.

#### DISCUSSION

DR HARRY FOERSTER, Milwaukee. I recall having seen this patient previously, and I favor a diagnosis of pemphigus erythematosus. The absence of bullous lesions during this long interval is a point against a diagnosis of true pemphigus vulgaris and also a recommendation of acetarsone therapy, which she has received during this time.

DR HERBERT RATTNER. I am not certain of the diagnosis in this case but there is a history of "pemphigus," from which the patient has recovered, and she complains of intense burning and itching. In fact, she emphasizes the complaint of burning. The distribution of the lesions is generalized and symmetric with a tendency to grouping. I wonder if this may not be a form of Duhring's disease, one of the severe types that Dr O'Leary has discussed at former meetings.

DR M H EBERT. I do not recall the history, has sulfapyridine been tried?

DR S ROTHMAN (by invitation). Sulfapyridine was tried without effect. She was treated for a long time with the diagnosis of dermatitis herpetiformis.

DR S W BECKER. I presented a young Italian boy who had been at the Cook County Hospital with what was diagnosed as pemphigus foliaceus. He was very ill in the hospital for several months and ill at home for several months. When I first saw him he presented lesions similar to those seen in the patient shown today and vegetative lesions behind the ears. The disease cleared, and it was concluded that his disease was an atypical dermatitis herpetiformis. I think that is what this woman has.

DR M H EBERT. Personally I believe the whole picture of erythema and infiltration on the face is that of a different disease. It is hard to reconcile it with a diagnosis of dermatitis herpetiformis.

DR EDWARD A OLIVER. This to me is not the picture of dermatitis herpetiformis. It is a more exaggerated picture than that seen in Duhring's disease. I believe that the case belongs somewhere in the cases of the pemphigus group, although it is not ordinary pemphigus. I should like to suggest that she be given vitamin D in large doses.

DR S ROTHMAN (by invitation). I will follow Dr Oliver's suggestion and give vitamin D a trial.

When I first saw this patient she had typical lesions of psoriasis on the elbows and knees. In addition, she displayed the circinate erosions of the same type as those seen today. After an observation of three months, during which I was unable to make a diagnosis and considered mainly dermatitis herpetiformis, large bullae and a strong Nikolsky sign suddenly developed. When she was presented here, pemphigus erythematosus and pemphigus foliaceus were considered as possible diagnoses. Bullae continued to develop for three months, but she has not had any new ones since July 1943. Possibly the bullous eruption was suppressed by the large doses of acetarsone which were administered continually at that time. The circinate and seriginous lesions continue to appear, grow and disappear. Sulfapyridine and dihydrotachysterol had no beneficial effect.

#### Monilethrix Presented by DR C M SMITH JR

A white girl aged 14 states that her hair was normal until she was 3 years old, when she had measles. At that time the hair became thin, with the greatest loss over the occiput. The hair has not returned appreciably since then. There is no history of disturbance of the hair in other members of the family.

Examination shows a large diffuse loss of hair from the scalp, and the remaining hairs have a definite beaded formation, which can be easily determined by palpation with the fingers. Examination by long wave ultraviolet rays showed the absence of fluorescence common to fungous diseases.

On examination the blood was essentially normal. The basal metabolic rate was +7.5 per cent. The cholesterol content was 170.

#### DISCUSSION

DR A B HANINGSLA (by invitation). The microscopic appearance of the hairs suggests that one should consider a diagnosis of pili torti. It might be a good idea to examine the hairs with polarized light.

DR M J REUTER, Milwaukee. I searched diligently but could not make out beaded hairs, although Dr Smith assures me that they are present. The thing that struck me was the presence of inflammatory papules of keratosis pilaris. Possibly this disease may be a manifestation of vitamin A deficiency.

DR E M SMITH JR. Vitamin A deficiency must be thought of. In the specimen presented there was a great deal of beading of the hair.

#### Alopecia Cicatricata (Pseudopelade [Brocq]) Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS

M H, a woman aged 60, presents on the scalp, involving the vertex, a general coin-sized patchy loss of hair with atrophy in the involved patches.

There are epidermic cones plugging the hair follicles in scattered areas in the immediate vicinity. The eruption has been present for nine months and is devoid of any subjective sensations. The family history is noncontributory.

#### A Case for Diagnosis (Lupus Erythematosus of the Scalp?) Presented by DR CLARK W FINNERUD

Mrs A M, aged 54, complains of loss of hair of the crown of three months' duration. There have been no subjective symptoms. The general history was non-

contributory aside from the fact that she had had a hysterectomy several years ago and that she takes E-lax for constipation

The examination shows alopecia of most of the crown, there being only small areas where hair is present. The scalp over the crown is atrophic and is mottled brown, red and yellowish white. Throughout the area keratotic plugging of the follicle mouths is present, extending well into the temporal and parietal regions. There is no evidence of eruption on the face or ears, in the mouth or elsewhere.

The Wassermann reaction was negative. Histologic sections showed conditions somewhat compatible with lupus erythematosus, there being hyperkeratosis of the stratum corneum, keratotic plugging of the hair follicles, slight epidermal atrophy in places and in places slight vacuolar degeneration of the basal cells. There was a rather dense cellular (large lymphocytes) infiltration of the corium, chiefly perivascular, perifollicular and periglandular.

#### DISCUSSION OF THE TWO PRECEDING CASES

DR JAMES H MITCHELL. I did not see the sections but I had the impression that Dr Finnerud's patient has pseudopelade. On palpation the atrophy felt like pseudopelade. The absence of characteristic lesions on the face and about the ears seems to point to that.

DR S W BECKER. I am sorry that I did not see the sections. I have had some patients for whom the differentiation was between lupus erythematosus and pseudopelade, and each time the disease turned out to be pseudopelade.

DR HAMILTON MONTGOMERY, Rochester, Minn. I agree with Dr Mitchell that Dr Finnerud's patient probably has pseudopelade, although I prefer the term "folliculitis decalvans" because histologically there is inflammation about the base of the hypertrophic keratotic hair follicles with liquefaction degeneration in these areas. There is no inflammatory reaction in the rest of the dermis or epidermis, which, together with a relative absence of inflammatory changes seen clinically, would speak against the diagnosis of lupus erythematosus.

DR M H EBERT. I think that Dr Finnerud's patient does not have pseudopelade because the arrangement of the atrophic areas is not of the type seen in pseudopelade. I am more inclined to think of lupus erythematosus. It reminds me of cases you see for years. Sometimes the follicles are more inflammatory, then the erythema disappears, leaving atrophy. At one time one thinks that the disease is lupus erythematosus, and at another time, pseudopelade. In this case, with the keratotic plugging of the area involved, I rather favor a diagnosis of lupus erythematosus than folliculitis decalvans.

DR JAMES H MITCHELL. The curving of the finger tips and the lesions over the crown strongly suggest pseudopelade to me rather than lupus erythematosus. Usually in such cases there will be one area with much more superficial scarring.

DR EDWARD A OLIVER. The case presented by Dr Omens seemed to me to be a typical case of pseudopelade, the one presented by Dr Finnerud I thought was a case of lupus erythematosus.

DR H M BULEY, Champaign, Ill (by invitation). If I understood correctly, the duration of the disease in Dr Finnerud's patient was three months. I do not think it is possible for lupus erythematosus to produce an atrophy as extensive as in this case in so short a

time without showing clinical signs of inflammation. That may be seen, however, in pseudopelade.

DR C W FINNERUD. Dr Omens' patient has pseudopelade. I saw the patient I presented for the first and only time one week ago. We performed a punch biopsy. We labeled the diagnosis sheet "pseudopelade" first and "lupus erythematosus" second. After seeing the sections, with the keratotic plugging and the character of the infiltrate, I could not imagine such a picture's being produced histologically by pseudopelade. From the history I should not even think of folliculitis decalvans. I presented the case with a questioned diagnosis. I think that the disease is lupus erythematosus.

#### A Case for Diagnosis (Superficial Glossitis)

Presented by DR HERBERT RATTNER

Mrs S H, aged 23, was admitted to the Gardiner General Hospital on Dec 6, 1943, complaining of soreness of the tongue. Her present complaint dates back to 1938, and since then she has sought medical relief with but little success. At present the soreness of her tongue is not acute. It was only during her pregnancy three years ago that she had little or no trouble whatsoever. Before being admitted to the Gardiner Hospital the patient was under the care of the dermatologic clinic of the University of Chicago. A telephone conversation with Dr Evangeline E Stenhouse revealed that the biopsy report showed no unusual conditions and that by administration of riboflavin, nicotinic acid and vitamin C and psychotherapy the lesions of the tongue receded.

The family history is essentially noncontributory. A review of her past medical history throws no light on her present complaint. Except for the lesions on the tongue, the physical examination revealed essentially normal conditions.

The laboratory data were all within normal limits. The Kahn reaction was negative. Scrapings from the tongue cultured on Sabouraud's medium yielded no fungi.

The patient has received no therapy at this hospital.

#### DISCUSSION

DR EVANGELINE E STENHOUSE. This patient has been under my care. She was referred by her own physician, who had given her large doses of vitamins both orally and by injection, and two series of injections of mapharsen intravenously. She was also under observation at the dental clinic of the University of Chicago. Because of the fact that the tongue improved during pregnancy, she was given an estrogenic preparation to apply locally. The patient states that the preparation makes her tongue feel more comfortable. When I first saw her, two or three months ago, the tongue was twice the size it is today and covered with large eroded areas. It was difficult for the patient to swallow and to eat. It has gradually improved, but new areas keep developing, such as is present on the right side of the tongue today. About three weeks ago she went west to be with her husband, and some physicians at the base hospital observed the area in the center of the tongue and told her that she had leukoplakia and should have radium treatment immediately. She came back here, and I assured her there was no leukoplakia. A biopsy from the center and from the area on the left side of the tongue showed superficial glossitis with erosion.

DR S ROTHMAN (by invitation). I should like to consider factitious erosions in the differential diagnosis. According to the history these lesions last for about

six weeks and then heal quickly. I do not know whether the patient is hysterical, but the history and the clinical picture suggest this possibility.

DR L. F. WEBER I would suggest Moeller's glossitis.

DR HAMILTON MONTGOMERY, Rochester, Minn. I suggest the possible diagnosis of aphthous stomatitis and that food tests be made to ascertain whether or not the patient is sensitive to chicken, wheat or other substances, as is sometimes the case. I do not believe that this is a dermatitis factitia. Patients who are sensitive to foods may also have an associated ulcerative or erosive dermatitis of the uvula, but this is not necessary.

DR EDWARD A. OLIVER I am inclined to agree with Dr. Ebert that there seems to be considerable atrophy of the tongue. It has persisted for a long time with remissions and exacerbations of the symptoms, and, as Dr. Weber has suggested, the diagnosis of Moeller's glossitis should be considered.

DR JAMES H. MITCHELL The lack of sensitivity was not in keeping with Moeller's glossitis.

DR M. H. EBERT It was my impression that this patient's tongue looked exactly like that of a patient whom Dr. Ormsby has observed for years and who has what is known as Moeller's glossitis, but that patient had a great deal of pain in the tongue at times. Does this woman suffer pain at times?

DR EVANGELINE E. STENHOUSE At first, for five or six months when the disease was acute, she had pain.

DR M. H. EBERT I think that Dr. Fred Harris described the disease as producing pain.

DR HERBERT RATTNER I saw this patient for the first time and for but a few minutes this morning. The eruption is an unusual one, and so I thought it best to present her today, while there was the opportunity. It seems that drugs as a source of the glossitis have been ruled out. The possibility of food sensitization, to my knowledge, has not been investigated, and I shall recommend such a study. I can recall 1 case in Dr. Pusey's practice in which severe glossitis was due to eating oatmeal. The possibility that the disease might be an example of Moeller's glossitis occurred to me, but I am not familiar with the entity.

**A Case for Diagnosis (Lichen Simplex Chronicus?)** Presented by DR F. E. SLIFAR, DR M. R. CARO and (by invitation) DR C. H. STUBENRAUCH, JR.

M. B., a white man aged 53, has had an eruption for about twenty years which has persisted without much change. He does not complain of itching, and he denies that he rubs or scratches his skin.

There are large patches on the face, sides of the chest, flanks, inner surface of arms and flexor surface of the forearms which are not sharply circumscribed. Within these areas the skin is thickened and dull red, with atrophy in the patches on the chest. During the period that he has been under our observation there has been no appreciable change produced in the dermatosis by the use of starch lotion, tar ointment or an ointment containing 40 per cent sulfur.

The examination of the blood showed 80 per cent hemoglobin, 3,950,000 erythrocytes and 7,500 leukocytes, with a differential count of 34 per cent lymphocytes, 4 per cent monocytes, 60 per cent neutrophils and

2 per cent eosinophils. The urinalysis showed normal conditions. The Wassermann and Kahn reactions were negative.

Histologic examination of a biopsy specimen from the left forearm showed acanthosis and edema of the epidermis. In places the edema was pronounced, and in one place a microscopic vesicle had ruptured. There was a dense cellular infiltrate in the upper part of the corium composed largely of lymphocytes, which in places invaded the epidermis. There was a slight infiltrate about the deeper vessels. There were a few strands of elastic fibers present beneath the epidermis, but these fibers were missing from the infiltrated areas and were fragmented deeper in the corium.

A biopsy specimen from the right flank showed many ballooned cells scattered throughout the epidermis, especially in the basal layer, edema of the papillae, a narrow horizontal layer of cellular infiltrate in the subpapillary zone containing many lymphocytes and a few eosinophils and a densely packed mass of cells about a hair follicle. The elastic fibers were fragmented throughout the corium.

#### DISCUSSION

DR HAMILTON MONTGOMERY, Rochester, Minn. This case is unique in my experience and the most interesting one presented at this meeting. There are definite areas of telangiectasia, atrophy, and pigmentation on the trunk, which suggest poikiloderma or possibly acrodermatitis chronica atrophicans. The diffuse erythema of the face would fit in with either disease. The absence of lesions on the legs would not rule out acrodermatitis chronica atrophicans. Most of the cases reported in the literature as instances of poikiloderma vasculare have proved on further observation to be examples of beginning or end stages of various dermatoses, from forms of lymphoblastoma to dermatomyositis, lupus erythematosus and lichen planus. Dr. Oliver some years ago emphasized this, as did Dr. Otto Foerster. The sections show relatively little change in the histologic appearance of the epidermis, and there is no flattening of the rete ridges as in acrodermatitis chronica atrophicans. There is, however, a definite border zone between the epidermis and the infiltrate and the cutis, which suggests an acrodermatitis. This is against the diagnosis of poikiloderma, in which condition liquefaction necrosis of the epidermis is usually seen. I believe this case warrants further observation and further histopathologic studies before a definite diagnosis can be made.

DR M. H. EBERT I was so struck by the poikiloderma-like character of the lesions that I thought of the possibility of lymphoblastoma, but I think that the long duration rules against it. I should like to hear Dr. Oliver discuss this case, in view of the fact that he had a patient who had the poikiloderma lesions for a considerable period.

DR EDWARD A. OLIVER While there may be some superficial resemblance in this case to my case of mycosis fungoides with poikiloderma-like symptoms, I do not believe that this case belongs in that group of cases. In none of the patches is there the telangiectasia, atrophy and other symptoms observed in that group.

DR M. R. CARO This case was also puzzling to us. Clinically we considered all of the diseases mentioned as well as pityriasis rubra pilaris in the differential diagnosis. The histologic picture is not diagnostic for any dermatosis with which I am familiar. We have been unable to come to any definite conclusion.



**Milroy's Disease** Presented by DR E M SMITH JR

A white man aged 22 has a chronic hypostatic edema of both lower extremities which has been present since birth. The edema does not pit and can be reduced by elevation of the legs or a prolonged stay in bed. The swelling is a little more noticeable in summer than in winter and is not made worse by exercise. Several of the toes show papular excrescences which appeared at the age of 12 years.

The mother has a similar condition of the lower extremities, which the patient states is proportional in degree to his own. His only brother's legs and ankles are normal, and there is no trace of this disturbance as far back as his mother's great grandparents.

The roentgenographic examination showed no abnormal conditions.

## DISCUSSION

DR WILLIAM A ROSENBERG (by invitation) The case reminds me of one I reported some time ago (ARCH DERMAT & SYPH 42:1113-1121 [Dec] 1940) from Northwestern University. The patient came to the clinic complaining of swelling and edema of her feet. The examination further revealed a congenital strabismus with amblyopia of the left eye, dystrophy of the hair and absence of several teeth. I reported her case as an instance of Milroy's disease associated with congenital anomalies.

DR E M SMITH JR I wonder what would happen if one were to remove some of the excrescences on the toes, whether it would produce oozing or not.

**Circumscribed Scleroderma** Presented (by invitation) by DR S ROTHMAN and DR Z FELSHER

J W, a 25 year old machinist, first noticed three "dark spots" in the left lower abdominal quadrant

about five years ago. These lesions slowly enlarged and became confluent. Six months after the onset he noted a similar lesion in the upper part of the left axilla. Later several other patches appeared on the trunk and extremities. Within the past few months, the patient had complained of general "muscle cramps," which are immediately relieved on motion and appear while he is at rest.

There is a sharply circumscribed large lesion of firm elastic consistency in the left lower quadrant of the abdomen, which ends sharply in the midline. Within this firm area there are hyperpigmented patches and pigmented atrophic spots, both devoid of follicular pores and hair. A similar but smaller oval area with a violaceous border is present on the left lower anterior part of the chest. Others are seen in the left axilla, right lower part of the chest, scapular regions, inner aspect of the right arm, back, and left thigh. There is no itching, and no pain is present in these lesions. The segmentary arrangement is conspicuous. The patient has an occupational oil acne. The basal metabolic rate was -7 per cent. The sedimentation rate was 13 mm. The Kahn reaction was negative. The examination of the blood yielded normal values.

## DISCUSSION

DR CLEVELAND J WHITE At the last meeting Dr Rothman asked about the results of bismuth therapy in some cases of scleroderma. I have had 2 patients with localized scleroderma who have done well with such therapy. Before treatment they looked like the patient presented today. I think that bismuth preparations are worth trying.

DR S ROTHMAN (by invitation) The little girl suffering from linear scleroderma whom I presented two months ago has improved considerably since she has received injections of a bismuth preparation.

## Book Reviews

A **Synopsis of Clinical Syphilis** By James Kirby Howles, B S, M D, M M S, Professor of Dermatology and Syphilology at Louisiana State University School of Medicine. Price \$6. Pp 667, with 121 illustrations and 2 color plates. St Louis. The C V Mosby Company, 1943.

This well bound booklet has a convenient size of 7½ by 5 inches (175 by 125 cm) and is printed in easily readable type on good glossy paper. The material is divided into three sections. The first section has nine chapters and deals with general considerations of syphilis. It contains material on the diagnosis, prognosis and treatment of acquired syphilis. Section II deals in twelve chapters with syphilis of the various organs and systems. Section III has four chapters, on the epidemiology of syphilis, on syphilis and pregnancy, on congenital syphilis and on organization of a syphilis clinic.

In the relatively small book the whole field of syphilis is thoroughly treated, there is also included

discussion and appraisal of recent subjects, such as massive arsenical therapy. In regard to the latter subject, the author shares the opinion of those investigators who consider this method of treatment to be still in the experimental stage, he states that it is still too early to determine the end results of treatment as well as all the dangers of this method, "which obviously are greater than those of the standard method of treatment." He considers the publicity given to massive arsenotherapy in the lay press as unfortunate and agrees with the writers who criticize it adversely.

On several occasions the author stresses the point that the treatment of all types of syphilis should be based first of all on the treatment of the patient and not of the disease. This point of view is the right one and is of such importance that in the opinion of the reviewer it cannot be often enough emphasized.

The author has succeeded in writing a synopsis of the whole field of clinical syphilis in a clear and brief way. It can be heartily recommended to the general practitioner as well as to the dermatosyphilologist.



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# Archives of Dermatology and Syphilology

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## THE ELECTRON MICROSCOPE IN DERMATOLOGY

GEORGE L. CLARK, PH.D., D.Sc., MARTHA BARNES BAYLOR, PH.D.,  
DOROTHY E. MARTIN, PH.D., AND GERTRUDE T. RAFFERTY, M.S.

URBANA, ILL.

One of the newest of all scientific instruments, which in only three years has a remarkable record for achievement, is the electron microscope. With it has developed an entirely new branch of physics known as electron optics. The present and the potential applications of electron optics and this powerful new instrument to the medical field of dermatology and syphilology are the subject of this brief preliminary paper. Electron micrographs obtained largely with the RCA instrument at the University of Illinois are used to illustrate the new facts of structures at high magnifications of cutaneous tissues of several kinds, individual cells and single protein molecules.

The University of Toronto, under the leadership of Prof. E. F. Burton, pioneered the development of this new science on this continent with a homemade equipment. There were only two or three other homemade installations in the United States prior to the arrival of the RCA electron microscope at the University of Illinois, just three years ago. There are now about forty of these RCA microscopes in operation in this country in the laboratories of universities, industries, hospitals and research institutions, besides other units which have been shipped abroad under Lend Lease.

A brief explanation of the theory, design, construction and operation of the electron microscope must suffice. Perhaps the most pertinent questions are why one has it and what it does that other methods or instruments cannot do. In microscopy, the concern is with resolving power, by which is meant how close together may two points be and yet appear as two separate, distinct points. The very best optical microscope available has a limiting resolving power of about 0.2 micron (1 micron = 0.001 mm), this value may be reduced to about 0.1 micron when ultraviolet rays are used for illumina-

tion and quartz instead of glass lenses are used in the microscope. Below this limit of resolution, or size of particle which can be observed, there has been no instrument capable of delineating smaller objects or fine structures of any material, although such methods as x-ray and electron diffraction indirectly led to measurements of a few ten millionths of a millimeter (or ten thousandths of a micron). When it was predicted by de Broglie in 1926 and then experimentally confirmed that a beam of electrons has a wavelength, just as light has a wavelength, but many times smaller even than that of ultraviolet radiation, the essential step was made toward the construction of a microscope with one hundred times the resolving power of any existent optical microscope. In other words, two points only 0.000001 mm apart (or 1 millimicron) should be clearly separated and then the size and shape of particles only one one-hundredth as large as any ever before observed be revealed. In the electron microscope, therefore, a beam of electrons from a hot filament, or "gun," and accelerated by voltages up to 60,000 volts takes the place of the beam of light usually reflected into ordinary microscope barrel by a mirror, magnetic fields produced by electric current in coils, fulfil the function of lenses instead of glass or quartz. Part for part, there is an exact analogy between the optical microscope and the electron microscope. The latter, however, further requires an extremely high vacuum, since air scatters the electrons, this means that moist and living specimens cannot long exist unchanged. Furthermore, the specimens must be exceedingly thin, since electrons are far more easily stopped than is light. Thus, the glass microscope slide is replaced by a collodion film only 10 millimicrons thick, which is picked up off a water surface as an invisible film and then supported on a tiny piece of 250 mesh wire gauze. The photographs are all made through one opening of this exceedingly fine gauze. The RCA electron microscope is a marvel of electrical and mechanical engineering, control must be so nearly perfect that the

From the Department of Chemistry, University of Illinois.

Read before the Section on Dermatology and Syphilology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 14, 1944.

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electrical circuits are very complex, for example, fifty-two vacuum tubes are required. Since the velocity of the electrons determines the wavelength and this must have as nearly as possible a single value, the high tension system produces a voltage of  $60,000 \pm 1$  volts, in itself a remarkable achievement. A direct magnification of nearly 30,000 diameters is obtained, and this image is then photographically enlarged to 100,000 to 125,000 diameters. The magnification of an image of comparable sharpness in the optical microscope is about 1,000 diameters.

the method of Cowdry. The ear was soaked for twenty-four hours in 10 per cent acetic acid. The skin was then peeled off in thin sheets, which then were either stained or mounted for optical microscopic examination or were stretched over the fine mesh screen mounting for the electron microscope. The stained preparations photographed with the optical microscope are seen in figure 1 *A* and *B*. The cell boundaries are clearly distinguished, and the nucleus appears dark (owing to the stain employed). Figure 1 *C* reproduces electron micrographs made at the same

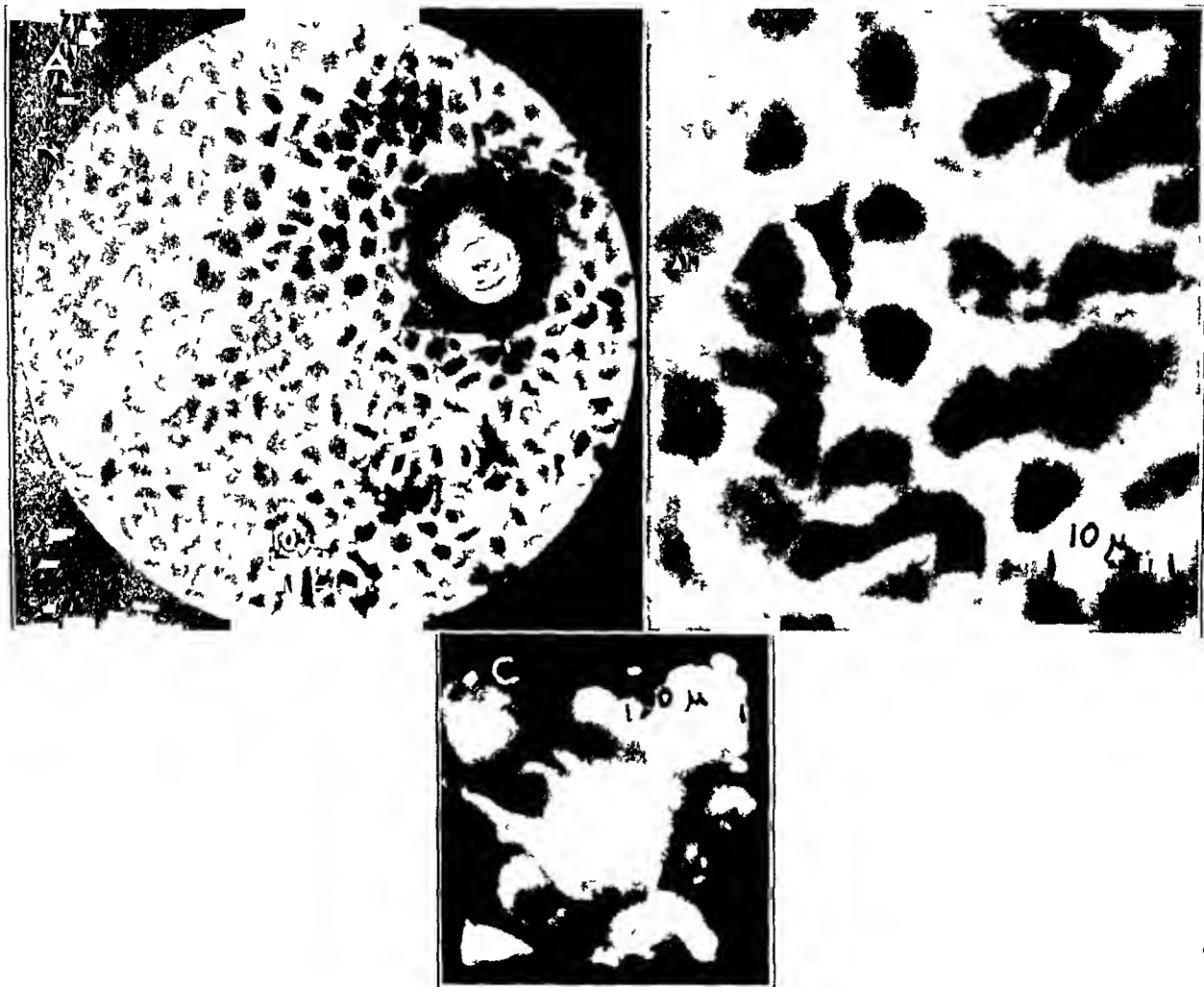


Fig 1—*A*, optical photomicrograph of surface layers of skin from a rat ear (480 diameters), *B*, optical photomicrograph of same preparation as in *A* at higher magnification (1,440 diameters), *C*, electron micrograph of surface layers of skin from a rat ear at the same magnification as *B* (1,440 diameters)

#### ELECTRON MICROGRAPHS OF SKIN

Thus far on the various electron microscopes in the United States very little work has been completed on the study of normal and pathologic skin structures, either epidermal or dermal. One of the limitations of the electron microscope is especially important in dealing with specimens of this type, namely, the extreme thinness which is required for penetration by the electron beam and for suitable resolution. The skin from the ear of an adult rat was prepared according to

magnification as the optical photomicrograph in figure 1 *B*. Again all boundaries and nuclei stand out clearly, and the detail is much sharper than that obtained with the optical microscope, thus illustrating the greater focal depth of the electron microscope. Figure 2 *A* is an enlargement of the same photograph, but here the sharpness and detail are diminished owing to the limitations of penetration. The electron beam is able to penetrate sections of 0.1 micron thickness, but the resolution diminishes as the section

becomes thicker. Figure 2 *B* is at a still higher magnification and with still poorer detail. Only the edge of the specimen can be penetrated, hence little information concerning the individual cells can be gained by this technique. Thinner sections are therefore essential if the cell is to be studied as such. At the very edges of the stretched membranes may be observed a structureless layer which is interpreted to be the thin

fibers. If such regularity of structure were present in the membrane, the resolution and magnification are entirely adequate to show this. In this very preliminary and limited observation of skin structure, it is evident that not a great deal has been added to the information available from the optical microscope and that effort must now be directed to the end of preparing much thinner tangential and cross sectional specimens,

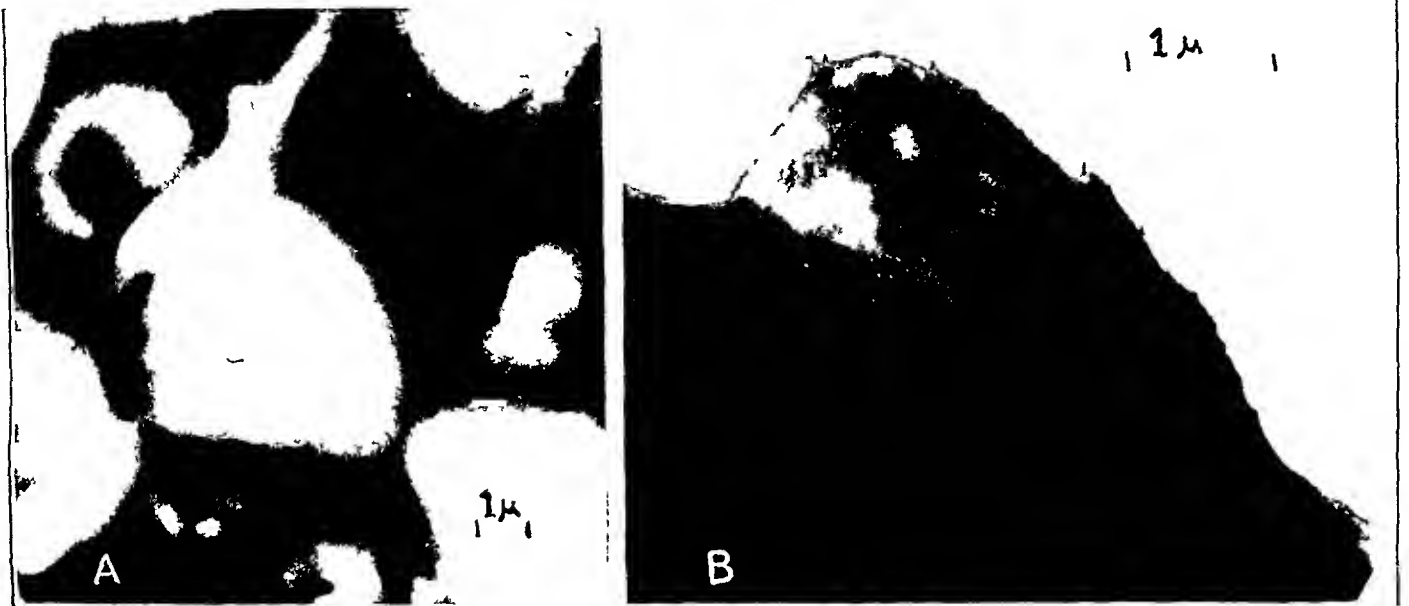


Fig 2—*A*, electron micrograph of same preparation as in figure 1 *C* at higher magnification, 4,300 diameters, *B*, electron micrograph of same preparation at edge, at magnification of 15,100 diameters

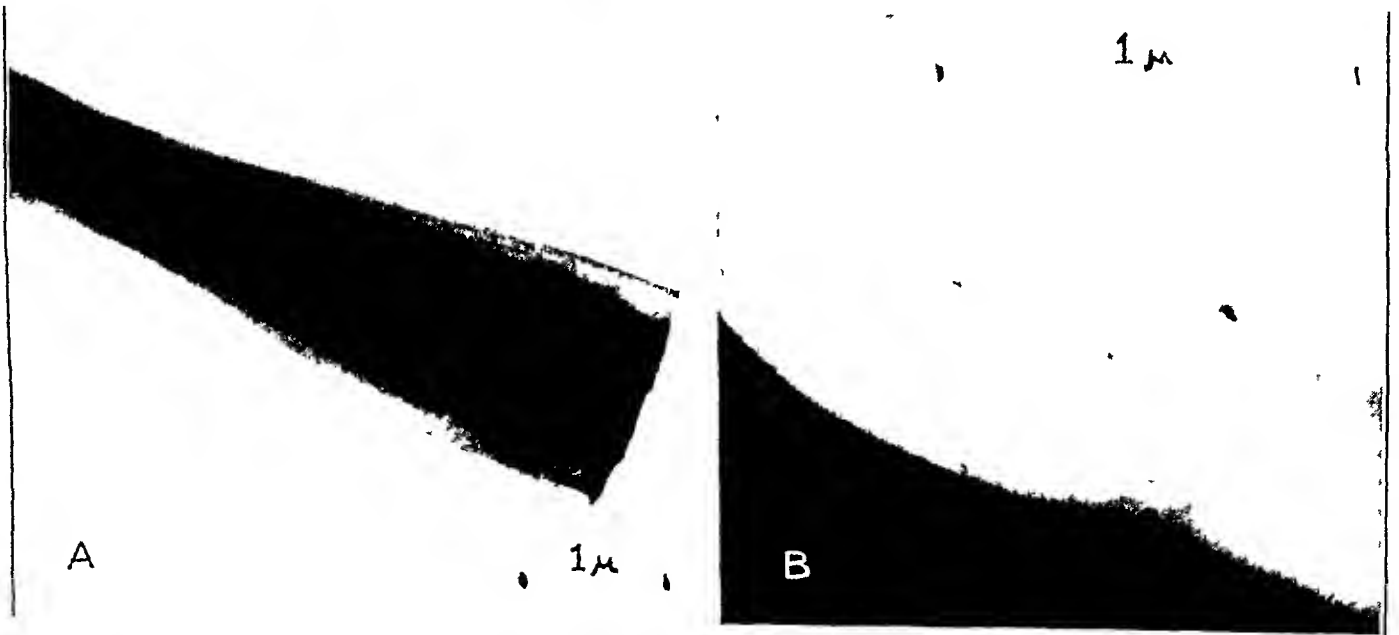


Fig 3—*A*, electron micrograph of thin sheet of keratinized membrane from stratum corneum (15,100 diameters) *B*, electron micrograph of thin sheet of keratinized membrane from stratum corneum curled up (43,125 diameters)

sheet of keratinized membrane from the stratum corneum. Figure 3 *B* shows at very high magnification this membrane stretched out in a sheet while figure 3 *A* shows the same extremely thin membrane curled up like a sheet of paper. Figure 3 *B* shows none of the long spacing periodicities of about 660 angstrom units or 66 millimicrons previously observed in collagen

research to this end is being continued in which various methods of cutting the specimens, including those frozen, are being worked out.

#### ELECTRON MICROGRAPHS OF OTHER TYPES OF TISSUE

Success has already attended the efforts to study several types of animal membranes and



tissues, especially those which are laid down in the thinnest and most delicate form and hence require no additional preparation for the electron microscope. The paper presenting the results of this study will illustrate the structure of butterfly wings, single filaments of spider web, insect trachea and air sacs, mosquito egg cases, which are only 0.01 micron thick, and cockroach cuticle.<sup>1</sup> These photographs illustrate a remarkable design of construction, with long parallel reinforcing filaments together with cross filaments like the rungs of a rope ladder. Studies of cockroach cuticle have led principally to the study of remarkable spiral tubes, of which there are 2,500,000,000 in the cuticle of each insect. These spiral tubes terminate not in the outer cuticle surface but at some distance below. Hence, they cannot be air or liquid vents, and

tion at a force greater than 1,500 times gravity led to a preparation on the collodion film which rested on the surface of distilled water so that salts were dialyzed through the film and the protein material was left on the surface. Figure 4 consists of optical photomicrographs of the cell constituents, indicating granules of two sizes without evidence of other materials. Figure 5A is an electron micrograph of these granules (which give a positive Feulgen reaction and must be nucleoproteins of the desoxyribose type) together with albuminous unoriented masses similar in appearance to dried egg albumin, and most interesting distinctly fibrous masses (fig 5B) which spray out into individual fibrils (fig 5C and D).<sup>2</sup> The diameters of the smaller fibrils in figure 5D are of the order of 0.025 microns. As further proof of the nucleoprotein

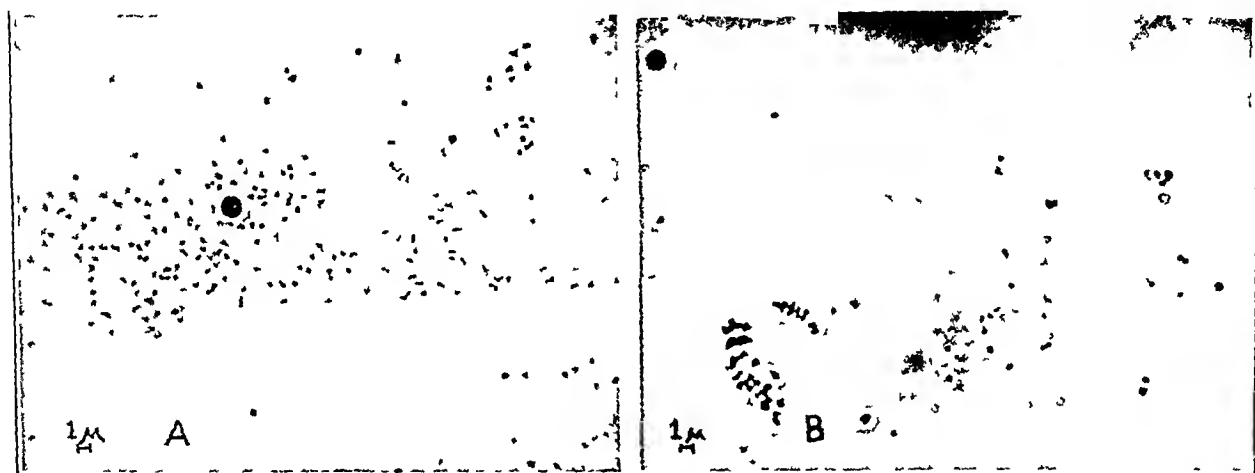


Fig 4—A, optical photomicrograph of cellular granules extracted by differential centrifugation (1,380 diameters), B, optical photomicrograph of cellular granules as in A but on another preparation

their function still remains a mystery. This discovery was made with the electron microscope of the University of Pennsylvania Medical School.

#### ELECTRON MICROGRAPHIC STUDY OF CELL CONSTITUENTS

The most fundamental problem in any biologic field is, of course, the structure of the individual cells. As typical of this type of investigation, a report is made of new work on the chromosome. Claude<sup>2</sup> in 1942 published a technique for extraction of chromatin threads from somatic cells. The materials were chick embryo and rat liver and spleen. Grinding with pure silica at 5°C in pure conductivity water followed by centrifuga-

nature and the chromosome origin, these materials were found to have the typical ultraviolet absorption at 2,600 angstrom units and the solubility in molar solution of sodium chloride and reprecipitation at 0.15 molar solution of sodium chloride, as found by Mersky and Pollister.<sup>4</sup> These photographs seem convincing evidence of the fibrillar nature of the chromosome.

Evidence of the axial fibrillar structure of sperm (bull and chicken) is shown in remarkably beautiful electron micrographs.<sup>5</sup> Especially significant is the fact that the tails spray out into ten fibrils.

3 A similar electron micrograph is provided by macerated actinomycotic granules, provided by Dr J H Lamb, Oklahoma City. These results will be published in detail later.

4 Mersky, A E, and Pollister, A W. Nucleoproteins of Cell Nuclear, Biol Symposia 10 247-261, 1943.

5 Baylor, M R B, Nalbandov, A, and Clark, G L. Electron Microscope Study of Sperm, Proc Soc Exper Biol & Med 54 229-232, 1943.

1 Richards, A G, Jr, and Anderson, T F. Electron Microscope Studies of Insect Cuticle, with a Discussion of the Application of Electron Optics to This Problem, J Morphol 71 135-183, 1942.

2 Claude, A, and Potter, J S. Isolation of Chromatin Threads from the Resting Nucleus of Leukemic Cells, J Exper Med 77 345-354, 1943.

ELECTRON MICROGRAPHS OF SINGLE  
PROTEIN MOLECULES AND  
VIRUSES

This laboratory has been fortunate in its excellent results in this field.<sup>6</sup> Several hundred measurements on electron micrographs of single molecules of Loligo peali (squid) hemocyanin yield an average value of 80 millimicrons for the diameter of the particles, which seem to be spherical. The molecular weight calculated is 216,000 which is exactly eight times the unit structural protein value of 27,000. Limulus

research a new phenomenon was observed. This is an agglomeration into microcolonies of the virus particles on the edges of bacteria which do not undergo destruction. This appears to be a defense mechanism set up by the bacteria to resist lysis. Cultures inoculated with lysate of integrated bacteria seem to have this flocculating and resisting power. In contrast, photographs will be shown of bacteriostasis with penicillin. The spirochete of syphilis with its flagella, photographed in several laboratories, will also be illustrated.

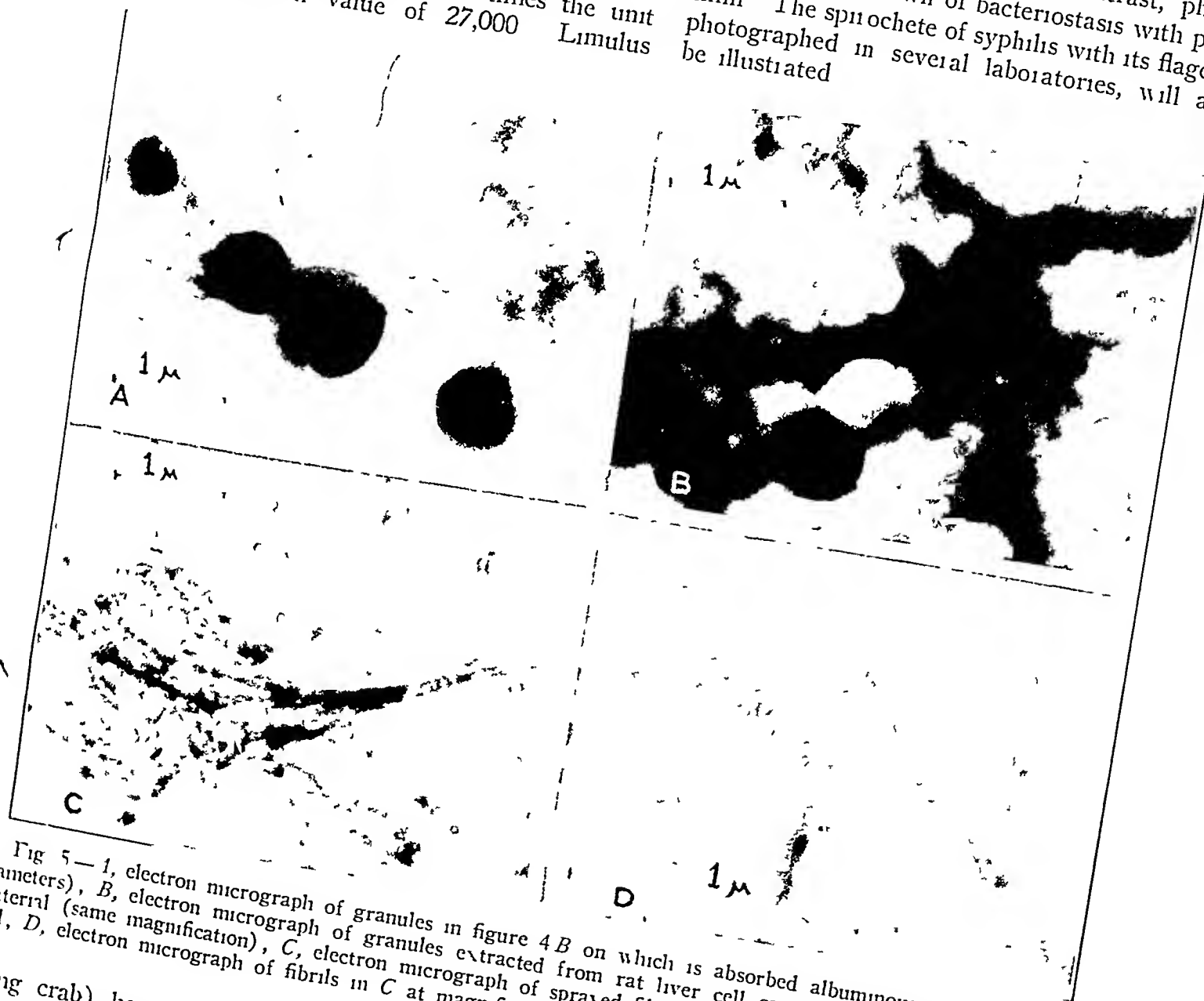


Fig 5—1, electron micrograph of granules in figure 4B on which is absorbed albuminous material (15,333 diameters), B, electron micrograph of granules extracted from rat liver cell carrying albuminous and fibrous material (same magnification), C, electron micrograph of sprayed fibrils constituting fibrous materials from the cell, D, electron micrograph of fibrils in C at magnification of 43,800 diameters

(king crab) hemocyanin has the diameter 17 millimicrons. Influenza virus particles have been measured several times and found to have a value of about 10 millimicrons. The bacteriophage of Salmonella pullorum has just been studied in this laboratory.<sup>7</sup> The size is 40 to 45 millimicrons. The characteristic lysis of the bacteria is clearly shown but in the course of the

## ELECTRON MICROGRAPHS OF COSMETICS

Returning again to the field of dermatology a subject of interest to dermatologists is the structure at magnifications of 100,000 diameters of the finest air-spun cosmetic face powder, of which many varieties have been photographed. The individual particles vary greatly in size and shape. Some seem to be thin flakes (fig 6) piled

<sup>6</sup> Clark G L, Quate M L, and Baylor M R B. Electron Microscope Studies of Proteins Including Some Hemocyanins and Nucleoproteins. *Biochimica* 4: 153-162 1943

<sup>7</sup> Baylor, M R B, Severens, J M, and Clark G L. Electron Microscope Studies of the Bacteriophage of Salmonella Pullorum, *J Bact* 47:277-285, 1944

one on top of another like the leaves of a book, others are rod like with sharp jagged ends or sometimes rounded ends (fig 7). One familiar brand consists of particles with a fearful array of sharp jagged hooks and spines. Correlations with cutaneous irritation is still lacking but

technic offer in attempts of identification of cellular components.

To answer this question, the bacterium *Rhizobium leguminosarum* was used as the test specimen for well known stains. The control shows intercellular inhomogeneities, the nature of which

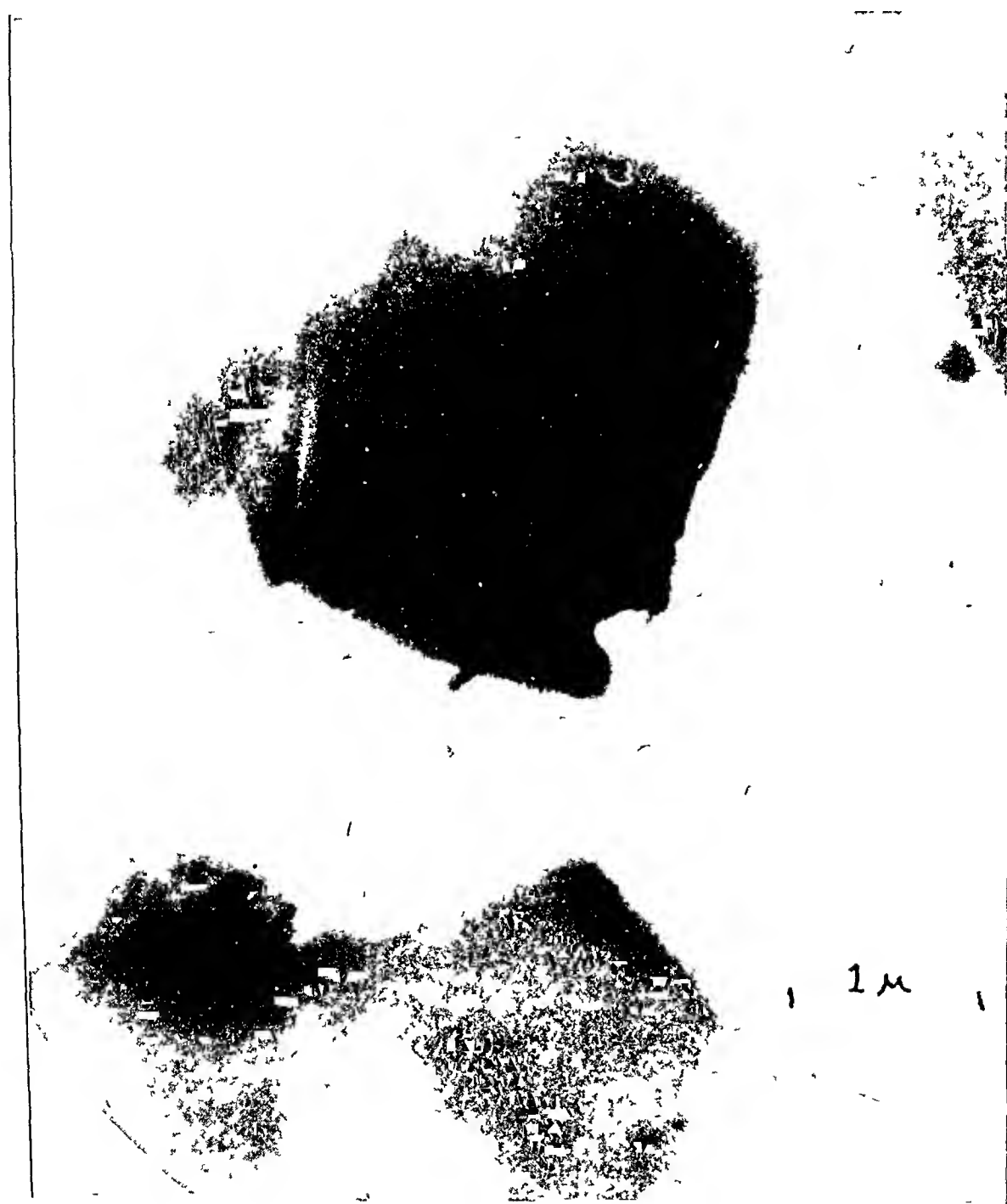


Fig 6—Electron micrograph of a widely used face powder at 25,000 diameters

surely a reexamination of the dermatologic effects of cosmetics is now indicated.

#### FIXING AND STAINING TECHNIQUES

Since it would be desirable to study animal tissues under the electron microscope, it has been asked what classic histologic fixing and staining

it would be desirable to know. Classic cytologic technics were employed, without hopes of gaining much information but with the idea that if the densities of certain materials could be increased or decreased differentially perhaps some clues might be gained. Since it must be for differences of density that one must look,

fixatives and stains containing heavy metal groups were employed. Also solvents which theoretically would remove differentially certain specific substances were tried.

With mercury bichloride as fixative, the cytoplasmic mass is shrunken and so dense that the electron beam cannot penetrate it. Silver nitrate

Cells soaked in solution of sodium bicarbonate for two and one-half hours present an interesting appearance. Mudd had reported that such treatment rendered the cytoplasm extremely transparent. Our micrographs confirm this observation for the granules stand out clearly. Meisky and Pollister expressed the belief that they had



Fig 7—Electron micrograph of another popular face powder at 25,000 diameters

shows a similar picture. Careful fixation with osmic tetroxide offers greater possibilities. Mayer's hematoxylin as a stain appears to be deposited heavily on the ghost cells but it does not differentiate any of the internal structure of the living cell. The same condition is found after staining with Heidenham's hematoxylin.

extracted the nucleoprotein of vertebrate tissues by soaking in 1 molar solution of sodium chloride. The extracted material shows the same physical properties (absorption bands in the ultraviolet, flow birefringence, etc.) as purified nucleoproteins. Slices of tissue show completely empty nuclei. Bacteria treated in this fashion

clearly show voids in the internal structure. However, treatment with sodium bicarbonate followed by sodium chloride exposed the granules which were hidden by the dense protoplasm. Soaking in sodium bicarbonate solution to clear the protoplasm followed by soaking in an organic solvent likewise does not remove the granules.

Acid treatment which precedes a Feulgen stain and has been claimed by Hiauysi and Mudd to remove nuclear granules has yielded nothing on the organism investigated in our laboratory.

These are but a few of the achievements and possibilities of the electron microscope as a new research and diagnostic instrument in the hands of the dermatologist. Only the barest beginning has been made on the skin itself, and that has been somewhat discouraging. However, there is not the slightest doubt that success will attend further efforts to prepare suitable specimens for examination at a magnification of 100,000 diameters. Unknown facts of the structure of skin will be revealed, and on this basis a great step



Fig 8—Electron micrograph of another popular face powder at 25,000 diameters

The Feulgen stain, which has been used by a German investigator with what he considered to be some success, has also shown nothing with either this organism or the salmonellas.

In general, classic cytologic technics have offered little to electron microscope preparations. The theory of differentially altering densities may still be valid, but much work correlating results of optical and electron microscopy is needed. However, the hopes held out by the new electron analyzer may remove the necessity of such detailed and tedious work.

forward in the science of dermatology can be made. Penicillin has been called the Cinderella of medical science, the electron microscope is the story of Alice in Wonderland.

#### ABSTRACT OF DISCUSSION

DR GREGORY SHWARTZMAN, New York. The electron microscope is a marvelous instrument. Dr Clark's new work is fully appreciated by those who are familiar with the difficulties found in its application to the fields of biology and medicine.

I believe that future progress may be aided by indicating not only the advantages but the limitations of this

new investigative approach. Dr. Clark has already done so. I shall only add some general statements in the light of my personal experience.

It is quite obvious that there exist two significant applications of electron microscopy in medicine: (a) observations on hitherto invisible viruses and (b) studies at greater magnification and resolution, on bodies already investigated with the light microscope. As physicians our interest is greatest in the first application, in view of medical importance of diseases caused by viruses.

The difficulties experienced with viruses come from the fact that they are obtainable only from infected animal tissues and therefore are necessarily contaminated with cell and tissue debris. Several investigators carried out extensive purifications of the viruses by chemical means, ultracentrifugation, etc., preliminary to examination.

In most of the studies the purified materials yielded round and oval bodies devoid of any morphologic characterization and similar to normal cell constituents, except possibly differing in size. In order to make the images clearer, Beard and his co-workers found it necessary to introduce another complicating factor—the addition of calcium chloride to the preparations.

Thus far, unfortunately, the drastic methods of purification of viruses have been in all probability responsible for the absence of typical morphologic characterization.

I don't want to state that the task of observing viruses with the electron microscope is a hopeless one; I merely wish to point out that new methods for purification and separation from the tissue debris must be worked out. I shall illustrate this point by relating shortly my personal efforts in this direction on the virus of the lymphocytic choriomeningitis. In preliminary studies, it was observed that the virus may be easily adsorbed on glass surfaces. This observation made then possible the purification of the virus without causing great damage to the virus itself. Thus, a section of the infected brain was brought into contact with several hundred capillary tubes, the fluid was removed immediately, and the capillaries were washed with Locke's solution.

Now, these washings were water clear, contained very little nitrogen, were highly infective and showed bodies of characteristic appearance.

Thus it seems that those methods have to be chosen for purification which are likely to cause the least morphologic damage; otherwise, the greatest advantage of the instrument may be lost.

The observations by Dr. Clark clearly demonstrate how valuable the results may be if the methods of preparation are well selected and applied to suitable materials. By the same token, new fields come into view—only to draw your attention to the striking photographs of chromosomes, the fine structure of spermatozoa and his most valuable observations on cosmetics.

The studies on intact cells and tissues, as pointed out by Dr. Clark, are still complicated by the necessity to obtain extremely thin films and by the fact that the high vacuum in which the examination is made may produce coagulation of certain proteins.

In my studies on bacteria and viruses, the films mounted on specimen holders were dried in vacuo from the frozen state and quickly introduced into the microscope. Coagulation was frequently avoided, clearer images were obtained, and not infrequently viable microorganisms could be recovered after exposure to the electron beam. The limitation was, however, in the fact that the low temperature frequently produced some crystallization of cell constituents distorting their appearance.

To sum up, broadly there are two approaches to electron microscopy. Some investigators approach it as physical chemists, with disregard for morphology. Their interest is to determine the diameter of the particles observed. Since better methods exist for determination of size, such as electrophoresis, which represent a large mass of particles, it is obvious that this approach does not bring about the best advantage of the electron microscope. Others, however, approach the field as microscopists with respect for and interest in morphology, and this is the manner in which Dr. Clark approached the subject.

DR. GEORGE L. CLARK, Urbana, Ill. There has been a great deal of, one might say, ballyhoo about the electron microscope, and much of it has been, I think, unfortunate, but those of us who are working with it are enthusiastic, we believe in it, we believe in its great possibilities and we hope that next year and in the years to come we may have the privilege of reporting again the progress that we are able to make in the field of dermatology.



# CHROMOBLASTOMYCOSIS

REPORT OF THE FIRST CASE OBSERVED IN THE CANAL ZONE

MAJOR JAMES S. SNOW, CAPTAIN E. S. WEDDING AND

MAJOR WRAY J. TOMLINSON

MEDICAL CORPS, ARMY OF THE UNITED STATES

Although chromoblastomycosis is a comparatively rare disease, it has been reported from widely scattered points on the globe. In 1941 Weidman and Rosenthal<sup>1</sup> summarized this subject thoroughly, including the data on 110 cases reported up to that time. Seven cases were from the continental limits of the United States, but the greatest number were from the Caribbean area (Cuba, Puerto Rico and Costa Rica) and Brazil. Since then additional cases have been reported from Cuba by Pardo-Castello, Leon and Trespalacios<sup>2</sup> and from the Union of South Africa by Simson, Harington and Barnetson.<sup>3</sup> Moore, Cooper and Weiss<sup>4</sup> have recently reported 2 additional cases from the United States. We wish to report the first case recognized in the Canal Zone and cultural studies of the causative fungus.

## REPORT OF CASE

D. M., a 74 year old Jamaican, came to the Canal Zone in 1915 and was employed as a carpenter until 1935, when he started farming. He was first seen at Gorgas Hospital on April 12, 1943, because of two verrucous lesions of the left ankle. He stated that this eruption had started about two years previously on the back of the heel and recalled that he had "jabbed" this heel on the thorn of a black palm "several months" before the first lesion appeared. A few months later a similar lesion developed on the outer aspect of the left ankle. Both of these were present when he had an intracranial hemorrhage necessitating admission to the hospital for care. After admission a third lesion appeared on the inner aspect of the left heel. The lesions were tender, especially when touched by his shoe.

The original and largest lesion (fig 1) was over the achilles tendon of the left heel and measured 2 by 4 cm.

From the Dermatology Department of the Medical Service and the Board of Health Laboratory, Gorgas Hospital, Ancon, Canal Zone.

1 Weidman, F. D., and Rosenthal, L. H. Chromoblastomycosis. A New and Important Blastomycosis in North America, *Arch. Dermat. & Syph.* **43**: 62 (Jan) 1941.

2 Pardo-Castello, V., Leon, E., and Trespalacios, F. Chromoblastomycosis in Cuba, *Arch. Dermat. & Syph.* **45**: 19 (Jan) 1942.

3 Simson, F. W., Harington, C., and Barnetson, J. Chromoblastomycosis. A Report of Six Cases, *J. Path. & Bact.* **55**: 191 (April) 1943.

4 Moore, M., Cooper, Z. K., and Weiss, R. S. Chromomycosis (Chromoblastomycosis), *J. A. M. A.* **122**: 1237 (Aug. 28) 1943.

The lesion on the outer aspect of the ankle just below the external malleolus was 2 cm. in diameter, and the one on the inner side of the heel was 1 cm. in diameter. The lesions were sharply defined, elevated and verrucous, and were firm and hard to the touch. They were dry, and no ulceration or pyogenic infection was present. When a biopsy was made, the tissue was hard, almost cartilaginous.

On April 13 and again on April 27, 1943 tissue was removed for microscopic examination and culture. On May 20 the 3 lesions were removed by curettement and electrodesiccation. Healing was slow owing to the location of the lesions and the age of the patient. By July 31 the lesions on each side of the heel were healed but there was still a crust on the large lesion over the achilles tendon. When seen Oct. 23, 1943, several small nodules were present along the upper border of this large lesion, and the patient was readmitted to the hospital. The recurrent lesion over the achilles tendon was curetted, and it was found that the entire scar area was undermined. This entire area (15 by 35 cm.) was thoroughly curetted, and the base was craterized with the actual cautery. The lesion healed slowly, and on December 11 there was only a thin dry scale present. When seen Jan. 15, 1944 this was entirely healed, and all three lesions are still healed, seven months after the last treatment.

## HISTOLOGIC EXAMINATION

There was pronounced epidermal hyperplasia and edema with elongation of the intrapapillary pegs. In these pegs were many small granulomatous abscesses (fig. 2) containing from three to five small dark brown sporelike structures measuring 12 to 15 microns in diameter. The abscesses contained neutrophils, small lymphocytes, plasma cells and some epithelioid giant cells. None of the sporelike bodies were contained in the giant cells. There were scattered areas of abscess formation throughout the papillary layer of the dermis, and many of these contained the sporelike brown bodies.

## CULTURAL STUDIES

After the diagnosis was established by histologic examination, macerated fragments of tissue were cultured on Sabouraud dextrose agar and dextrose-yeast extract mediums.<sup>5</sup> Sets of

5 Kurung, J. M. The Isolation and Identification of Pathogenic Fungi from Sputum, *Am. Rev. Tuberc.* **46**: 367 (Oct) 1942.

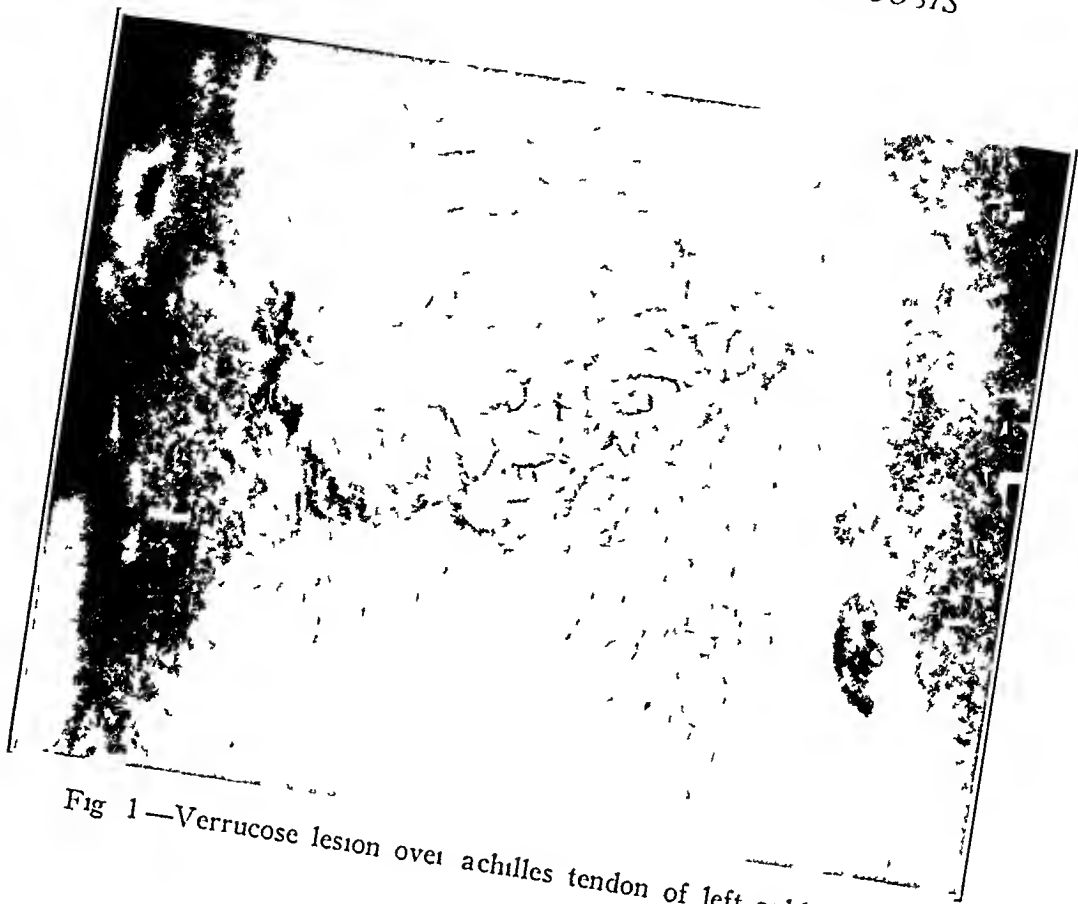


Fig 1—Verrucose lesion over achilles tendon of left ankle  $\times 2$



Fig 2—Sporelike bodies in intrapapillary abscess  $\times 540$

cultures were kept at 100m temperature and others were incubated at 37.5 C

*Results of Cultures*—No growth occurred on the original Sabouraud medium. In seven days an olive green growth appeared on the dextrose-

up to 0.7 cm in diameter and presented a firm green-brown umbo and a green-black base, with extension of this color into the medium. At two months, the colonies measured up to 2.5 cm in diameter, were green-black and had irregular

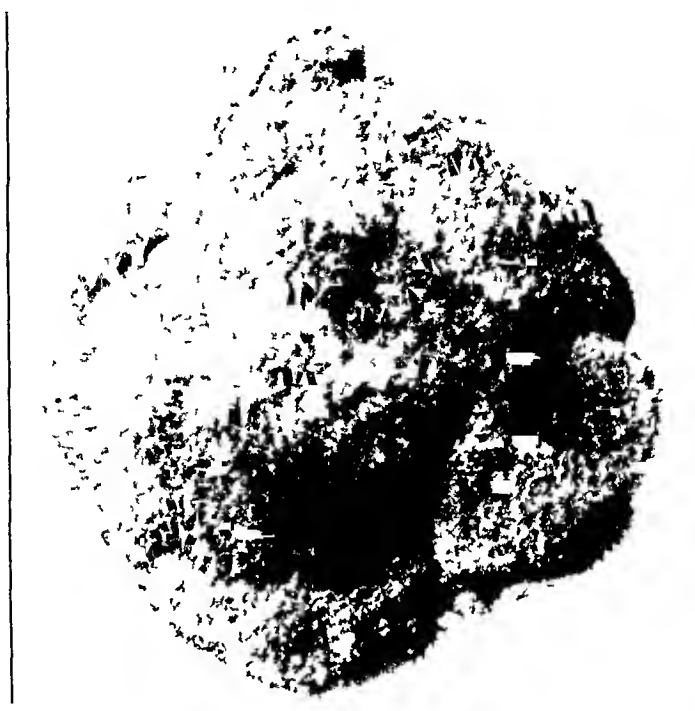


Fig 3—Appearance of a two month colony of *F. pedrosoi* var. *communis* grown on Sabouraud dextrose agar  $\times 3$



Fig 4—Photomicrographs of variations found in *F. pedrosoi* var. *communis*. A, hormondendrum variant  $\times 750$ , B, acrotheca variant,  $\times 750$ , C, philalophora variant,  $\times 750$ , D, aberrant form,  $\times 750$

yeast medium in the incubator, cultures at 100m temperature on this medium showed growth three days later. Transfers from the dextrose-yeast medium to the Sabouraud medium grew well.

*Gross Appearance of Colonies*—After two weeks the colonies were black-green, measured

crowns and edges (fig 3) extending slightly into the medium. The hyphae were repent, short and somewhat powdery.

*Microscopic Appearance of Fungus*—The hyphae were septate, with occasional racket-like structures. The predominant method of sporula-

tion was an acrotheca arrangement (fig 4B), and a few phialophoras were observed (fig 4C). Extensive search was necessary to demonstrate a few hormondendrum heads (fig 4A).

*Classification of the Fungus* The fungus recovered resembles *Fonsecaea pedrosoi* var *communis*, showing the integrating forms (fig 4D), which probably, according to Carrión,<sup>6</sup> represent connecting types between the other three varie-

ties described by him, namely, *F. pedrosoi* var *typicus*, *F. pedrosoi* var *cladosporioides* and *F. pedrosoi* var *phialophorica*.

#### SUMMARY

This case of chromoblastomycosis is the first case of the disease reported from the Canal Zone. The fungus recovered was classified as *F. pedrosoi* var *communis*. The lesions have remained healed seven months after removal by curettage and cauterization.

6 Carrión, A. L. Chromoblastomycosis, abstracted, Trop Dis Bull 40:410 (May) 1943.

# NODULAR NONSUPPURATIVE PANNICULITIS (WEBER-CHRISTIAN DISEASE)

PRELIMINARY REPORT OF A CASE CONTROLLED BY SULFAPYRIDINE

HARRY L. ARNOLD JR., M.D.

HONOLULU, TERRITORY OF HAWAII

The most recent reports of relapsing febrile nodular nonsuppurative panniculitis indicate that up to now the disease has not been found to respond to any treatment. Miller and Kritzler<sup>1</sup> in 1942 reported the first autopsy on a patient dying of this disease; they had given their patient sulfanilamide, sulfathiazole and sulfadiazine successively with only transient benefit from sulfanilamide. They decided in retrospect that even this benefit was merely apparent and that the sulfonamide compounds were of no value. Sulfapyridine was apparently not tried. Christian's recent edition of Osler's textbook,<sup>2</sup> which shortens the name to "relapsing febrile nonsuppurative panniculitis," contains the statement that "treatment should be symptomatic" and does not refer to any reported successful treatment or mention the use of sulfonamide compounds. Larkin, De Sanctis and Margulis,<sup>3</sup> in February 1944, reviewed the literature and reported the twentieth case of the disease; they mentioned disappointing results from eradication of foci of infection but did not otherwise touch on treatment. Their own patient recovered spontaneously in about six months. I have found no more recent references than these.

The purpose of this report is to present a typical case of this disease in which sulfapyridine effectively controlled all of the signs and symptoms over long periods.

## REPORT OF CASE

M. H., a 27 year old Caucasian stenographer, was first seen in March 1943, because of an eruption limited

Read at the Staff Meeting of The Clinic, Honolulu, June 1944.

1 Miller, J. L., and Kritzler, R. A. Nodular Nonsuppurative Panniculitis, *Arch. Dermat. & Syph.* 47:82 (Jan.) 1943.

2 Osler, W. The Principles and Practice of Medicine, edited by H. A. Christian, ed. 14, New York: D. Appleton-Century Company, Inc., 1942, pp. 472 and 1187.

3 Larkin, V. de P., De Sanctis, A. G., and Margulis, A. E. Relapsing Febrile Nodular Nonsuppurative Panniculitis (Weber-Christian Disease), *Am. J. Dis. Child.* 67:120 (Feb.) 1944.

to the anterior part of the left thigh, consisting of moderately tender, slightly raised, hazelnut-sized deep-seated cutaneous nodules (fig. 1). It had been present and slowly spreading for about four months. The entire involved area felt "knobby." Mantoux tests with 0.00002 and 0.005 mg. of purified protein derivative of tuberculin elicited negative reactions at forty-eight hours, and Kolmer-Wassermann and Eagle reactions of the blood serum were negative. A biopsy failed to



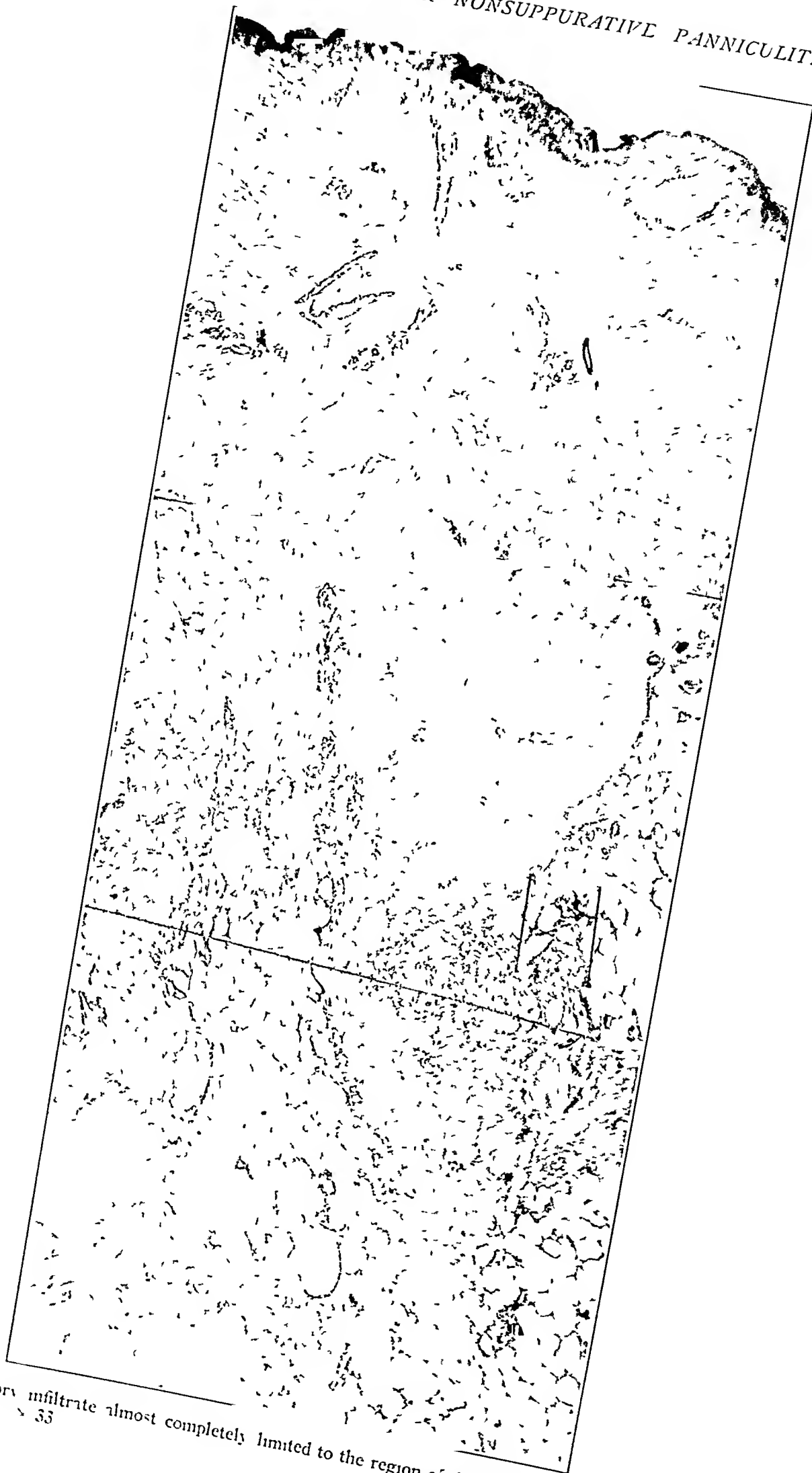
Fig. 1—"Marbled" and knobby appearance of the left thigh and two lesions above the right knee. Note the peculiar hirsutism in the involved areas.

show significant histologic changes. Sulfadiazine and then sulfathiazole were given, without benefit.

The patient returned almost two months later, somewhat worse. General physical examination, including fluoroscopic examination of the chest, revealed nothing of note except a pulse rate of 108, a temperature of 99 F and moderate diffuse abdominal tenderness. Gynecologic examination showed that this might be explained by ovulation on the left. Otologic consultation, including roentgenograms of the sinuses, showed no significant disease; there was a septal perforation, possibly a sequel of a nasal operation performed eighteen years before.

In June a second and more extensive biopsy was performed (figs. 2, 3 and 4). This showed a deep-seated inflammatory process centering around arterioles and

ARNOLD—NODULAR NONSUPPURATIVE PANNICULITIS



2—Inflammatory infiltrate almost completely limited to the region of the upper part of the fatty panniculus  
xlm and eosin x 33



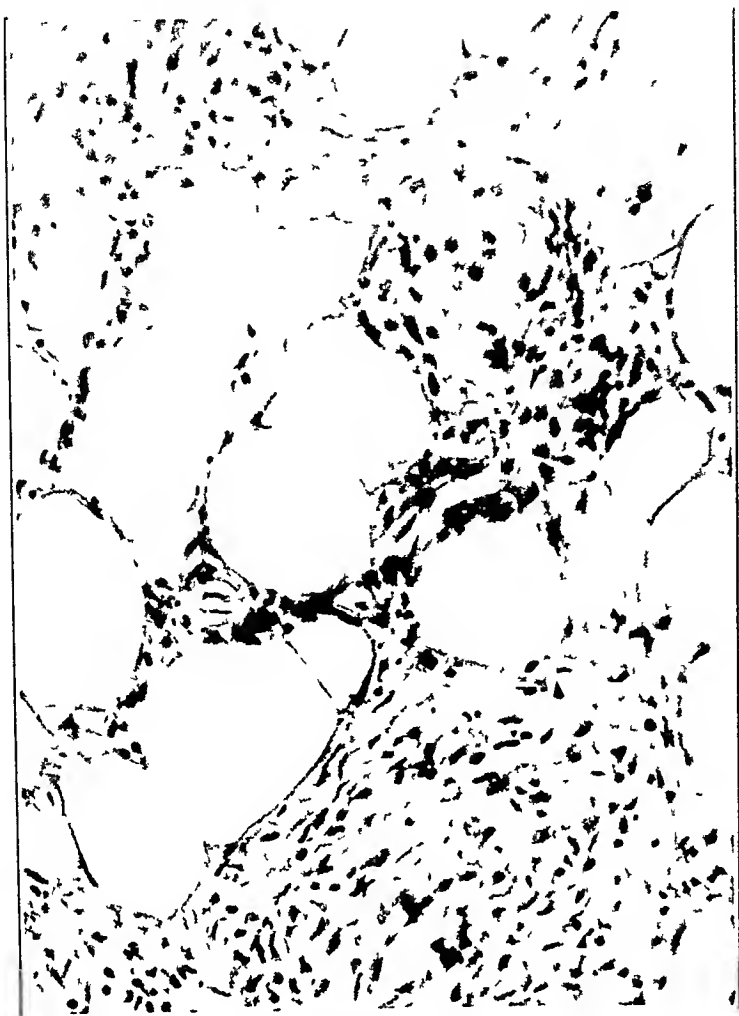


Fig 3—Fat-loaded macrophages ("lipophages") and arteriolitis Hematoxylin and eosin,  $\times 300$



Fig 4—Epidermal atrophy and fibrous replacement of collagen in a healed area relatively near the surface Hematoxylin and eosin,  $\times 130$

arteries and involving the subcutaneous fat. The vessels showed intimal thickening, with occasional obliteration of the lumen and recanalization in places, round cell and polymorphonuclear infiltration and fibrous replacement of portions of the subcutaneous fat, there were several typical macrophages with foamy cytoplasm in the vicinity of the latter process. The relatively high proportion of fibrosis to inflammatory and phagocytic reaction suggested that the lesion selected for biopsy may have been a mature one, already beginning to undergo involution. One section of the epidermis showed atrophy and depression below the surface, strongly suggestive of the depression of healed lesions which is often seen clinically in patients with nonsuppurative panniculitis but which was inconspicuous in this patient.

Two months later the patient returned, reporting that she was much worse, the lesions were slightly more extensive, and though they were still limited largely to the left thigh, isolated nodules had developed on the forearms, chest and opposite thigh. She was feeling too tired to work and was spending much of her time in bed. All the symptoms were aggravated during menses. The white blood cell count was now 12,100, as compared with 10,000 per cubic millimeter in April and May, the differential count was still normal, with slight eosinophilia. The urine contained albumin (1 plus). The cholesterol level of the blood was 180 mg and serum protein level 7.3 Gm per hundred cubic centimeters. The Weltmann coagulation band, which had been 5 (minimal shift to the left) on May 24, was now, two months later, down to zero, suggesting extensive and severe exudative disease.

At this point administration of sulfapyridine was begun orally in a dose of 1 Gm five times a day, with an additional 3 Gm as the initial dose. Three days later her temperature was normal (it had been over 100 F daily), the lesions were all bluish, cool to the touch and less tender, and the patient felt decidedly improved, except for slight malaise which seemed attributable to the drug. The sulfapyridine level of the blood was 117 mg per hundred cubic centimeters. Two days later it had risen to 147 mg, the Weltmann reaction was still zero, the sedimentation rate (modified Westergren method, normal 2 to 5 per cent), which had been 15 per cent in May and had risen to 35 per cent on July 30, had dropped to 27 per cent. Clinical improvement was continuing. Two days later, after nausea had interrupted the medication for thirty-six hours, the blood level of the drug had fallen to 97 mg per hundred cubic centimeters, many recent lesions had completely healed, and all the lesions had greatly improved.

Three days later the dose of sulfapyridine was reduced to 0.5 Gm five times daily because of vomiting, the blood level dropped to 49 mg per hundred cubic centimeters, and clinical improvement became slower and presently stopped. The Weltmann coagulation band had now risen to 5, and the sedimentation rate had dropped to 9 per cent. The dose of sulfapyridine was slightly increased, to 4.5 Gm a day, with a prompt increase of the blood level to 11 Gm per hundred cubic centimeters and immediate resumption of clinical improvement.

Late in September a recurrence of an old cardiospasm prevented the ingestion of the drug for a few days and there was an immediate increase of size, redness and warmth in several lesions, and two new ones appeared on the back. On resumption of the drug these all subsided promptly.

On October 15 use of the drug was purposely stopped and the patient had a prompt relapse, with recurrence

of cutaneous lesions, elevation of temperature, increase of sedimentation rate from 4.5 per cent to 12 and then to 21 per cent and rise of white blood cell count from 5,100 to 9,750 and then to 12,750 over a period of two weeks. The Weltmann reaction, however, remained at 6 (normal) during this period and subsequently. The sulfapyridine level of the blood dropped to zero by the end of the first week. Resumption of the drug was followed as before by prompt remission of symptoms and signs.

On December 6 use of the drug was purposely stopped for the second time, as before, relapse was prompt and within a week virtually complete, also as before, the lesions were neither so extensive nor so severe, and the patient was not so sick as she had been prior to the administration of the drug. Resumption of sulfapyridine again produced prompt remission of all symptoms and signs. Toward the end of January the Weltmann reaction, which had remained at 6 since late in September, rose to 7, while the sedimentation rate fell to 4 per cent.

On February 7 administration of sulfapyridine was again discontinued. This time the relapse was not apparent at all until the fifth day and was not well established till the eighth day, even then it was comparatively mild. On the fourteenth day the cutaneous lesions had nearly all recurred, but tenderness was moderate, limping was slight and the lesions were all smaller than before. The Weltmann reaction had dropped to 5, and the sedimentation rate had risen to only 13 per cent. On the eighteenth day the patient was limping badly and felt ill, the sedimentation rate had risen to 18 per cent and the white blood cell count to almost 12,000, with 72 per cent polymorphonuclear leukocytes and 6 per cent eosinophils. Sulfapyridine was again administered in a dosage of 3.5 Gm per day in divided doses.

Within two weeks the eruption had again disappeared, the sedimentation rate had dropped to 8 per cent, the Weltmann reaction had risen to 7, and the sulfapyridine level of the blood was 91 mg per hundred cubic centimeters. A month later, on April 11, the Weltmann reaction was still 7 and the sedimentation rate had fallen to 5 per cent—a normal level. The patient felt tired but otherwise well and was working regularly.

On May 19 the sulfapyridine was again discontinued, chiefly because the patient had been taking it continually for nearly three months. Relapse was prompt, occurring within three or four days, but mild, the lesions on June 6 were all well under 1 cm in diameter, the patient felt well, walked without limping, and was afebrile, and the sedimentation rate was only 23 per cent and the Weltmann coagulation band 5. She felt so well that she preferred, and was permitted, not to resume use of sulfapyridine.

#### COMMENT

The validity of the primary diagnosis in this case does not seem at all doubtful. The asymmetric distribution is unusual but not particularly remarkable, the absence of well defined depressed scars is probably attributable to the comparative profuseness and small size of the individual nodules, the relatively severe vascular damage in the sections is also unusual but has been reported before in at least 1 case, and, as Weidman<sup>4</sup> implied and as I have felt, the dividing

4 Weidman, F. D., in discussion on Miller.<sup>1</sup>

line between this disease and erythema nodosum is by no means a sharp or clearly defined one. Moreover, the patient has been seen in a relapse by Dr. H. M. Johnson, who originally suggested the diagnosis, and by six dermatologists in the Medical Corps of the Army of the United States,<sup>5</sup> all of whom concurred in the diagnosis.

That the response to the sulfapyridine, whatever its mechanism, has been a specific one seems almost equally clear. Initially it seemed possible that one was observing the antipyretic effect of the pyridine group rather than the action of the sulfonamide group, but now that five prompt remissions of symptoms and signs on administration of sulfapyridine and five immediate relapses on reduction of the dose or discontinuation of the drug, have been observed over a period of a year (fig 5), the specificity of action of sulfapyridine seems reasonably well established.

view, and I feel that it is equally applicable to the present case.

Larkin and his associates<sup>3</sup> reported that the literature failed to reveal any laboratory procedures that shed light on the clinical course of the disease. In this case I believe that both the sedimentation rate and the Weltmann reaction shed considerable light on it. The sedimentation rate regularly became elevated when the disease was in uncontrolled relapse, and the elevation was approximately proportional to the severity of the clinical signs and symptoms. The Weltmann coagulation band showed a maximum shift to the left before treatment was started and returned gradually to normal during treatment, during the relapses in December and February it shifted left (to 5) during the relapse, indicating exudative disease, and shifted right (to 7) during the subsequent therapeutic remission.

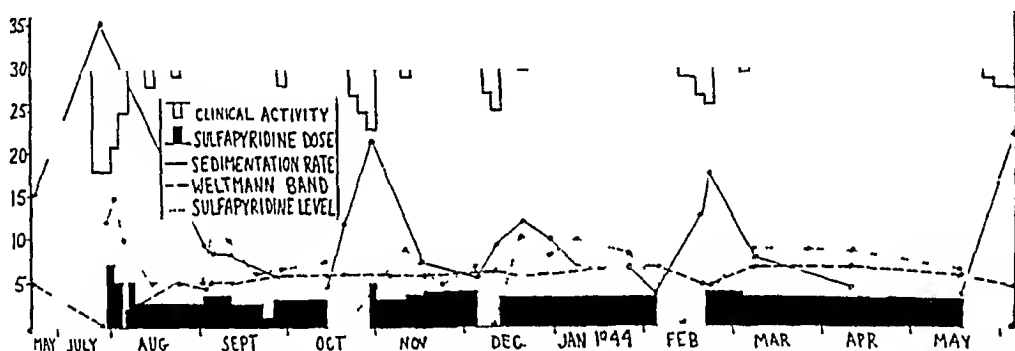


Fig 5—Relation of dosage and blood level of sulfapyridine to clinical activity and laboratory observations over a period of a year.

The temptation to regard this action as a specific one on a micro-organism is strong. Only one blood culture was made, and it was negative for pathogens, and no obvious focus of infection was found, yet a response to a sulfonamide drug offers rather strong presumptive evidence that an infection existed. Perhaps the weakest point in such an argument was the failure of the drug to produce remission of symptoms outlasting the period of its administration—in other words, to eradicate the infection, if there was one. However, Walter Lever,<sup>6</sup> in reporting control of a case of acrodermatitis continua (Hallopeau) by continued administration of sulfapyridine, concluded that the therapeutic response favored "the possibility that the disease may be caused by bacterial allergy." I am sympathetic with this

indicating fibrotic disease, presumably fibrosis, in the healing lesions. The Weltmann shift was neither sufficiently great nor sufficiently prompt, however, to be of much value in evaluating the patient's status at any given time.

It is interesting to note that dermatitis herpetiformis has generally been found to respond to sulfapyridine more regularly than to any of the other sulfonamide compounds,<sup>7</sup> for it, like Weber-Christian disease, is a chronic relapsing disease which is often aggravated by iodides or bromides or both and which—again like Weber-Christian disease—has been suspected of being caused by bacterial allergy.

#### SUMMARY

This is the twenty-ninth reported case of relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease).

<sup>5</sup> Meeting of Civilian and Military Dermatologists Practicing or Serving in Hawaii (unpublished transactions).

<sup>6</sup> Lever, W. F. Acrodermatitis Continua (Hallopeau), *Arch Dermat & Syph* 49:273 (April) 1944.

<sup>7</sup> Ormsby, O. S. Avitaminosis in Dermatology and the Value and Limitations of the Sulfa Group in Skin Diseases, *J Michigan M Soc* 43:315 (April) 1944.

This case has been observed for over a year, during which time the administration of approximately 3.5 Gm of sulfapyridine a day has kept the patient completely symptom free and her erythrocyte sedimentation rate within normal limits. On five occasions a relapse immediately followed discontinuance of the medication, and on each of these occasions a remission ensued within twenty-four hours of its resumption.

During clinical activity the erythrocyte sedimentation rate was elevated, and during clinical quiescence it returned to normal levels.

During clinical activity the Weltmann coagulation band was shifted to the left, at one time

to zero. During clinical quiescence it was shifted slightly to the right, as high as 7.

#### CONCLUSIONS

Relapsing febrile nodular nonsuppurative panniculitis may be on the basis of bacterial allergy in some cases.

The erythrocyte sedimentation rate and the Weltmann reaction are of value in evaluating the status of the disease.

Sulfapyridine may be effective in controlling all the outward manifestations of the disease, even when sulfathiazole and sulfadiazine have failed.

Dr. Irvn L. Tilden, of The Clinic, made the photograph and the photomicrographs.

The Clinic, 881 South Hotel Street, Honolulu 53

# CHRONIC DISCOID LUPUS ERYTHEMATOSUS WITH SUPERIMPOSED XANTHOMATOUS INFILTRATION

REPORT OF A CASE

EARL W NETHERTON, MD

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The occurrence of xanthomatous changes in lesions of a well established dermatosis is exceedingly rare. This process was thought by early investigators to be caused by fatty degeneration or pseudoxanthoma, in recent communications this type of xanthosis is classified with local lipidoses. This phenomenon cannot be differentiated from true xanthoma on the basis of chemical and histopathologic features, however, it differs clinically and probably in pathogenesis.

In classifying diseases of lipid metabolism, Urbach<sup>1</sup> suggested the term 'resorption xanthelasma' for this process and stated that it had been known to occur in scars of tertiary syphilids, herpes zoster, laparotomies and acrodermatitis atrophicans. More recently Urbach and Hill<sup>2</sup> supported the assumption that in generalized or essential xanthomatosis there is lipid infiltration, while resorption xanthelasma is an imbibition process. Instead of the lipids being derived from fatty degeneration of fibrous tissue, cells of diseased tissue absorb cholesterol and related lipids which have become separated from the blood at the site of the disease. They stated that in resorption xanthelasma the blood lipid level is normal.

In 1927 Weidman<sup>3</sup> advocated the use of the term "xanthosis," which was suggested by Siemens, to indicate the yellowing change induced by infiltration of tissue cells by cholesterol

and cholesterol esters, particularly when the changes were not manifestations of one of the well established xanthomatoses.

More recently Weidman and Boston<sup>4</sup> discussed at some length the tendency of xanthomatous infiltration to involve granulation tissue or inflammatory processes in which young fibroblasts are present. They observed that this phenomenon may occur in the presence or absence of hypercholesteremia or other manifestations of disturbed lipid metabolism of the whole organism and proposed the term "scar xanthoma" when scars are in any way involved in xanthomatous processes. In contrast to the concept of Urbach and Hill,<sup>2</sup> Weidman and Boston<sup>4</sup> stated the belief that the source of the lipid which induces xanthomatous infiltration in scars is not in itself important.

"Scar xanthoma" seems to be the preferable term. It satisfactorily describes the clinical manifestation of this unusual expression of xanthoma and does not possess the disadvantage of an assumption relevant to its pathogenesis.

Weidman<sup>3</sup> has shown that hypercholesteremia does not make certain the development of xanthomatous infiltration even in lesions containing young, rapidly dividing fibroblasts. He attempted to produce xanthoma by performing biopsies on 10 patients with hypercholesteremia. Five patients had diabetes, 1 of whom also had xanthoma. Another patient had xanthoma tuberosum. In no case did xanthomatous changes develop in the scars of the biopsy, and xanthoma cells were not observed in the specimens.

In animal experimentation Weidman was able to produce xanthosis only once. Dogs infected with pneumococci received large amounts of cholesterol by intraperitoneal injection to determine the value of cholesterol as a protection against pneumococcal infection in dogs. In 1

From the Cleveland Clinic

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 19, 1944

1 Urbach, E. Ueber Lipoidosen mit cutanen Erscheinungen, *Klin Wchnschr* **13** 577 (April 21) 1934, abstracted, Wise, F., and Sulzberger, M. B. Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1934

2 Urbach, E., and Hill, W. R. A Proposed Classification of Cutaneous Lipoidoses, with Description of a New Local Lipoid Dermatoses. Imbibito Lipoidica Collagenei Degenerata Cutis, *Arch Dermat & Syph* **42** 68 (July) 1940

3 Weidman, F. D. Studies in Hypercholesterolemia. III. The Approach to the Pathogenesis of Xanthomas, *Arch Dermat & Syph* **15** 659 (June) 1927

4 Weidman, F. D., and Boston, L. N. Generalized Xanthoma Tuberosum with Xanthomatous Changes in Fresh Scar of Intercurrent Zoster. Adenocarcinoma of Ampulla of Vater at Necropsy, *Arch Int Med* **56** 793 (May) 1937

dog hemorrhagic peritonitis yellowish red swelling on the elbows and severe edema of the scrotum developed Superficial crusted ulcers developed on the edematous scrotum Frozen sections of the scrotum and nodules on the elbows did not contain true xanthoma cells but did show histologic changes identical with those seen in the early stages of human xanthoma Weidman considered the experimentally produced xanthosis to be quite different from the disease xanthoma He concluded that xanthoma tuberosum depends on factors other than hypercholesteremia and young, rapidly dividing, connective tissue cells

They emphasized the need for searching for unknown factors in the pathogenesis of xanthomatous infiltration in scars.

Their patient was a man aged 44, whose illness began as generalized pruritus. Jaundice developed one month later, and during the fifth month of illness cutaneous lesions of xanthoma tuberosum began to develop on the elbows and knees on the rims of the ears and about the mouth. Later, lesions appeared on the palms and on the extensor surfaces of the arms, back and buttocks.

The Wassermann reaction of the blood was positive once but negative later. Old scars on

## Case Reports Reviewed by Weidman and Boston

All but 1 of the cases cited by Weidman and Boston have been reviewed and some additional information tabulated. Search for pertinent cases reported since 1937 has been made. A critical review of the literature on xanthomatosis has not been undertaken here, in recent articles on essential xanthomatosis this rare type of xanthosis is seldom considered.

Author	Sex	Age	Primary Lesion	Associated Xanthomatosis	Hypercholesterolemia
Kreibich	M	22	Herpes zoster (?) zosteriform arrangement of lesions	Xanthoma tuberosum	Present
Hordaway	M	44	Herpes zoster zosteriform arrangement of lesions	Xanthoma tuberosum	Not stated
Weldman and Stokes (Gittings)	F	3	Iaparotomy scar and gum following extraction of teeth	Xanthoma tuberosum	Present
Urbach	F	54	Nodular ulcerative syphilids	None	Absent
Posner	F	37	Iaparotomy scar	Xanthoma tuberosum Xanthoma palpebrarum	Not stated
Schmidt	F		Postoperative scar		Present ovarian dysfunction thought to influence lipids
Ochs	F	7	Vaccination scar and site of therapeutic antisyphilitic injection	Xanthoma tuberosum	Present
Major	M	16	Mosquito bites	Xanthosis diabetica	Present
Artom *		11	Herniotomy scar	Xanthomatous papules	
Pinkus and Peek	F	60	Erysipelas	Xanthoma tuberosum, Xanthoma of viscera, Xanthomatous meningitis	Present
Delizen and Knauss	F	9	Festers	Papular and nodular xanthomas	Not stated
Dehnen and Knauss	F	11	Vesicular eruption	Papular and nodular xanthomas	Not stated

\* This reference was not available

The cause and pathogenesis of xanthoma and scar xanthoma are unknown. These entities differ clinically but histopathologically are identical and in each the cellular metabolism of cholesterol and related lipids is disturbed. Therefore certain factors favoring the local deposition of cholesterol and its subsequent phagocytosis by intimoendothelial cells are probably fundamental and common to both processes.

Numerous reviews of the literature pertain to essential xanthomatosis but few discuss xanthomatous changes in preexistent dermatoses. Even more consideration is given to xanthosis of tumours, retention cysts and degenerative lesions

In 1937 Weidman and Boston<sup>4</sup> reviewed 12 cases of scar xanthoma in the literature and reported an additional case with xanthomatous changes in fresh scars of intercurrent zoster.

the scalp, arms and shins were considered to be sequelae of late noduloulcerative syphilids

There was decided hypercholesteremia Eight months after the onset of illness a zoster developed on the left side of the chest along the distribution of the seventh, eighth and ninth thoracic nerves One month later xanthomatous papules appeared in the scars of the zoster, and small follicular punctate yellow papules developed just below the lower lip The uniform spacing of the papules suggested to Weidman and Boston that the xanthomatous changes developed in microscopic scars caused by shaving Xanthomatous infiltration did not occur in the old syphilitic scars That xanthomatous changes occur in young scars which contain young, rapidly dividing cells of fibrous tissue rather than in old sclerotic scars was stressed by Weid-



man and his co-workers. This point is demonstrated in all cases in the literature.

Bechet<sup>5</sup> observed a 39 year old woman with a hypercholesteremia, an extensive xanthoma palpebrarum and xanthomatous discoloration throughout a large port wine nevus on the arm. A biopsy was not made, however, the discoloration apparently was caused by diffuse xanthomatous infiltration.

The xanthosis of the nevus in Bechet's case can best be explained on the basis of scar xanthoma occurring in a sclerosing vascular nevus.

Gross and Wolbach<sup>6</sup> recently studied the histopathology of sclerosing vascular nevus. Early in the process the intervascular tissue is very cellular and young fibroblasts are numerous. When phagocytosis of lipid is outstanding in the sclerosing process, the tissues become yellow and are microscopically similar to those seen in xanthoma. The sclerosing process occurs most frequently and the phagocytic properties of the reticular cells are more apparent in the capillary form of hemangioma. Cutaneous hemangiomas are more often involved than those of the viscera.

In 75 per cent of the specimens studied by Gross and Wolbach there was accumulation of lipids or hemosiderin or both in the sclerosed areas. In a few instances these substances seemed to come from hemorrhages within the angioma.

In March 1943 Anderson<sup>7</sup> presented a case before the Los Angeles Dermatological Society which was similar to, if not identical with the one reported herein. The case was presented with a provisional diagnosis of xanthoma.

The patient was a woman aged 52, with oval to annular raised erythematous plaques on each side of the neck and the upper portion of the chest. There were also two sharply demarcated raised, pink to red plaques on each malar region. The lesions extended to the outer canthus of each eye, and their upper margins had a distinct yellowish tinge. Reticulated erythema was present on the lateral surfaces of the arms. A biopsy showed fatty infiltration and xanthomatous changes. Two months later the patient was presented before the same society for the second time<sup>8</sup>. Further investigation revealed that she had nocturnal dyspnea and pain in her

chest. An electrocardiogram revealed that she had "heart trouble." The type of heart disease was not stated. The blood cholesterol level was normal.

Anderson was unable to classify his case as an instance of any of the recognized types of xanthomas, however, he stated the belief that the histologic changes were identical with those of xanthoma. In the discussion Goeckerman and Lindsay said that they believed that this was probably a case of lupus erythematosus showing xanthomatous degeneration. Goeckerman stated that he knew of 2 cases in which xanthomatous changes occurred in lesions of lupus erythematosus.

In March 1941 my associate, George H. Curtis, and I presented a patient before the Cleveland Dermatological Society<sup>9</sup> with a provisional diagnosis of xanthoma or of lupus erythematosus with xanthomatous infiltration. After further study I have concluded that it is an example of scar xanthoma occurring in lesions of preexistent chronic discoid lupus erythematosus. As far as I have been able to determine, this is the first case of xanthosis of chronic discoid lupus erythematosus to be reported.

This case adds one more dermatosis to the list of dermatologic entities in which scar xanthoma may occur and is reported in detail.

#### REPORT OF CASE

A nun, aged 45, came to the Clinic on July 2, 1940. Her chief complaint was an eruption on the face of ten years' duration. She had been told that she had lupus erythematosus and had received various types of treatment, without permanent benefit. Sulfamidamide therapy produced definite improvement but had to be discontinued after a brief period because of the patient's severe hypersensitivity to the drug.

During her youth she had had measles, mumps, varicella and pertussis. She had attacks of pleurisy and tonsillitis. Her tonsils were removed in 1930, and in 1936 a hysterectomy was performed. She seldom had headaches and had no symptoms referable to the cardiovascular system. She was never jaundiced, and her stools were always of normal color. Because of constipation she used compound pills of cascara habitually.

One of her sisters had tuberculosis, and four paternal uncles and one paternal aunt had died of diabetes mellitus.

About 1930 a red area appeared in the right malar region. This lesion gradually enlarged by peripheral extension, and other lesions appeared on the right side of the face. The original lesion finally became confluent with a smaller lesion, to form a large irregular plaque involving the anterior portion of the right side of the face. Recently small light red plaques appeared on the right side of the face and on the lower edge of the right ear.

9 Netherton, E. W., and Curtis, G. H. A Case for Diagnosis (Xanthoma? Lupus Erythematosus with Xanthomatous Infiltration?), *Arch Dermat & Syph* 45:440 (Feb) 1942.

5 Bechet, P. Xanthoma Palpebrarum with Xanthomatous Lesions in a Large Congenital Nevus Flammeus, *Arch Dermat & Syph* 25:752 (April) 1932.

6 Gross, R. E., and Wolbach, S. B. Sclerosing Hemangiomas. Their Relationship to Dermatofibroma, Histiocytoma, Xanthoma and to Certain Pigmented Lesions of the Skin, *Am J Path* 19:533 (July) 1943.

7 Anderson, N. P. A Case for Diagnosis (Xanthoma?), *Arch Dermat & Syph* 48:471 (Oct) 1943.

8 Anderson, N. P. Systemic Xanthoma, *Arch Dermat & Syph* 49:149 (Feb) 1944.

In 1937 similar plaques developed in the left malar region and on the left side of the face. Small, poorly demarcated erythematous areas recently appeared on the bridge of the nose. The lesion on the left side of the face also enlarged by peripheral extension, while the lesions on the nose remained the same. Since the onset, the lesions would become edematous and more erythematous when exposed to strong sunshine. This reaction was accompanied by a slight burning sensation.

The time of onset of gradual yellowing of the plaques was not known. Xanthosis of lesions was more rapid in the left malar region than in the older plaques.

Physical examination revealed hypertension (systolic pressure 170 and diastolic 90) and enlargement of the liver. The liver was smooth and not tender and extended about 3 fingerbreadths below the costal margin.

The eruption was strikingly symmetric, was limited to the face and right ear and had the butterfly distribution commonly seen in chronic discoid lupus erythematosus. The lesions consisted of fairly well demarcated raised, rounded and irregularly shaped, large and small plaques located in each malar region and on the sides

There was an oval depression, caused by tightly fitting spectacles, on each side of the base of the nose. The imprints showed none of the changes characteristic of the lesions on the face (fig 1).

A roentgenogram of the chest was normal. The urine was normal. The hemogram showed 4,520,000 red blood cells per cubic millimeter, 5,250 white blood cells and a hemoglobin content of 84 per cent. The differential count showed 53 per cent neutrophils, 7 per cent eosinophils, 38 per cent lymphocytes and 2 per cent monocytes. The Wassermann and Kahn reactions of the blood were negative. The blood sugar content three and three-fourths hours after eating was 106 mg per hundred cubic centimeters. On July 3, 1940 the fasting blood plasma cholesterol level was 200 mg per hundred cubic centimeters, and on March 27, 1941 four and one-fourth hours after eating it was 187 mg. A Mantoux test with tuberculin (purified protein derivative) in the first strength elicited a negative reaction and in the second strength a positive reaction.

On July 3, 1940 a biopsy specimen of the most xanthotic area was removed from the upper outer portion of the original plaque in the right malar region. In June 1941 a second specimen was removed from the

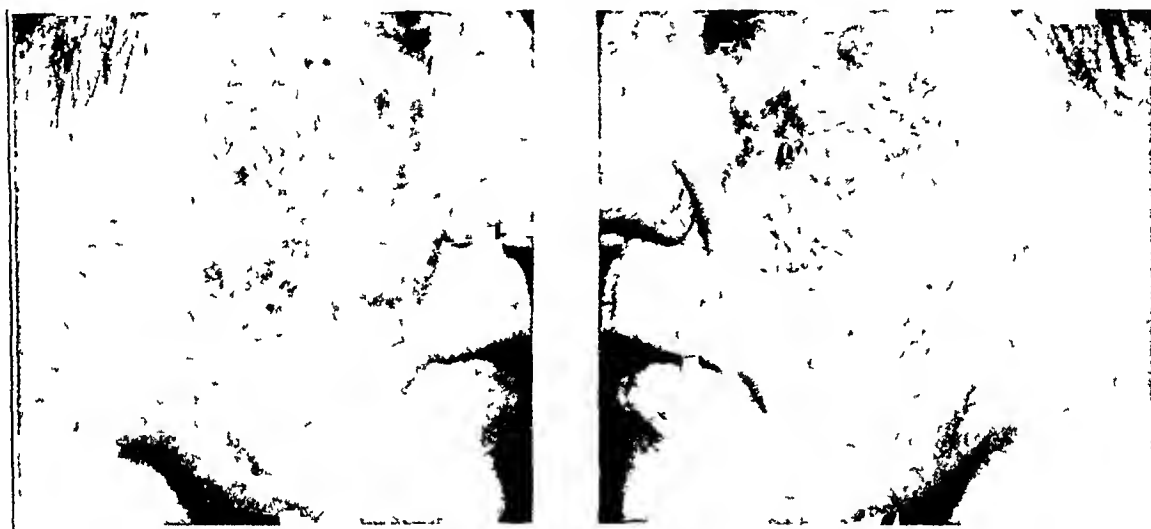


Fig 1—Symmetry and distribution of lesions frequently seen in discoid lupus erythematosus. Oval depressed areas on each side of the base of the nose were caused by eyeglasses and were not identified with the eruption.

of the face, bridge of the nose and lower edge of the right ear. The eyelids were not involved. In the malar region was a narrow peninsula-like projection of the margins of the plaques, which terminated near the outer canthus of each eye. The lesions varied from pink or light red to a distinct yellow. The smaller and younger lesions were pink or light red, while the larger plaques in the upper and central portion were yellow and the lower margins were erythematous. The central portion of the lesions in the malar regions was depressed and appeared to consist of xanthotic scar. The xanthosis of the eruption in the left malar region was patchy, thereby producing erythematous to yellow reticulation. Yellow discoloration was not so apparent in the smaller and younger lesions. The lesions on the bridge of the nose were small and not so sharply demarcated as those on the face. There was a small dry adherent scale on the lesion on the right ear. Other lesions were not scaly. In some areas the orifices of pilosebaceous follicles were dilated. A few small keratotic plugs were present in follicles of the plaque in the left malar region. It should be noted that follicular keratotic plugs were present in the lesion of three years' duration rather than in the older lesion, which had been present for ten years. Xanthosis was most pronounced in older plaques.

younger lesion on the left cheek to study the earlier histopathologic changes.

Tissue from the older lesion showed a uniform atrophy of the epidermis. There was a thin layer of hyperkeratosis, the granular layer was thin but intact, and the rete mucosa consisted of four to six layers of prickle cells. The basal layer was intact throughout all sections. Interpapillary pegs had been obliterated completely by changes in the corium. Only a few orifices of the pilosebaceous follicles were dilated, and these contained hyperkeratotic plugs. Except for one follicle the dilatations were not deep, and acanthosis adjacent to the dilated follicle, which is usually seen in discoid lupus erythematosus, was absent.

In practically all of the corium the normal connective tissue was replaced by cellular infiltrate consisting of lymphocytes, fibroblasts, epithelioid cells and large and small foam, or xanthoma, cells. Touton and endothelial giant cells were not observed. In some areas the interstitial stroma was delicate, while in others the stroma was more dense and fibrous and contained more mature fibroblasts and less cellular infiltrate. A few small foci of lymphocytic infiltration were present in the midportion of the corium and about the dilated pilosebaceous follicles. There were only a few atrophic sebaceous glands. The sweat glands were normal.

The foam cells varied considerably in size and were most numerous in the upper and central portion of the corium. Some dilated capillaries were surrounded by small foam cells.

Throughout the corium the small blood vessels were dilated. There was a hyperplasia of endothelial cells in the walls of many dilated capillaries. Small groups of endothelial cells could be traced to the walls of the

fat stains showed more follicular and perifollicular changes than those used for hematoxylin and eosin stains, consequently these features could not be studied to the best advantage.

Sections stained with sudan III and scarlet red showed a spotty intracellular and extracellular deposit of lipids scattered throughout the upper and middle portions of the corium. The uniform lipid infiltration

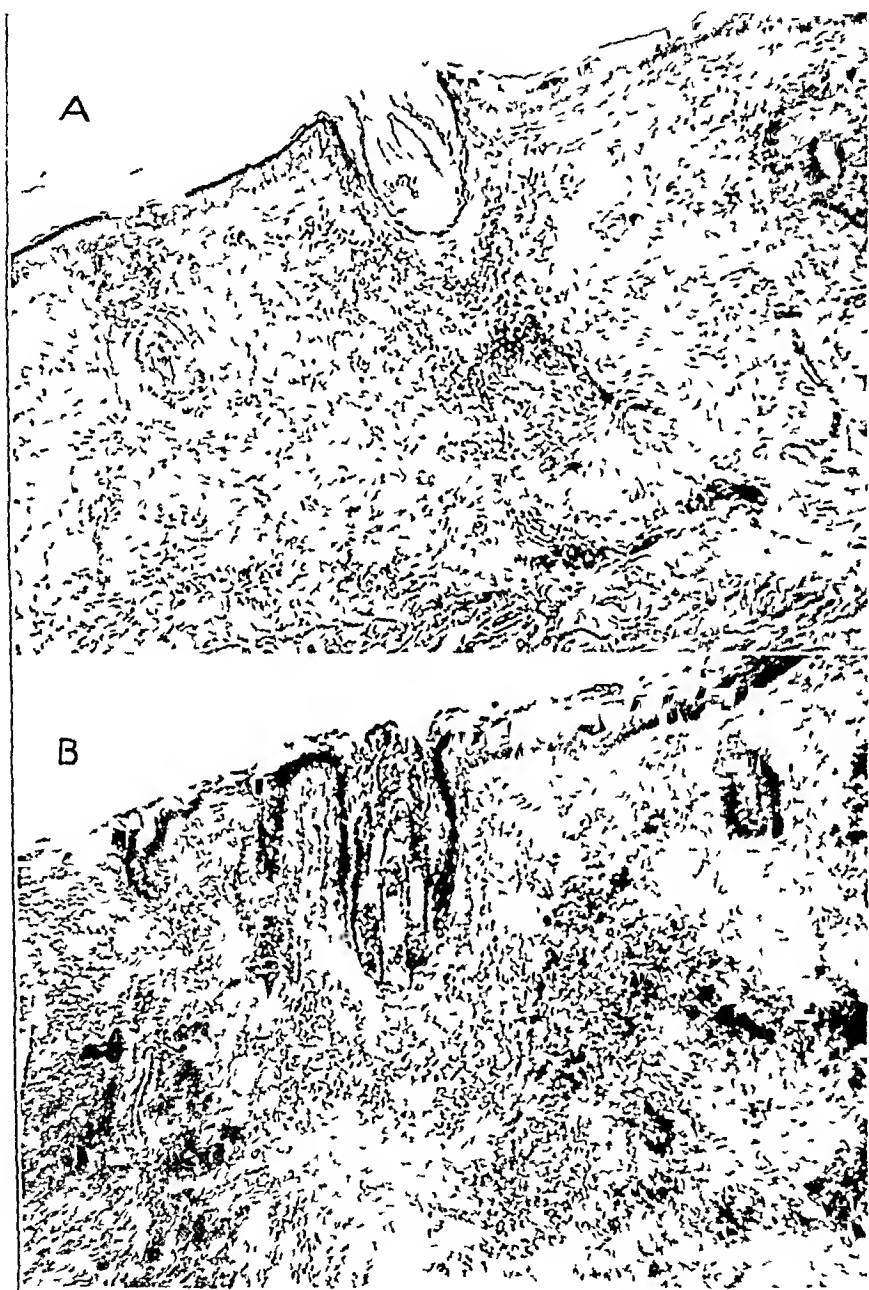


Fig 2—*A*, section from the oldest lesion, in the right malar region showing uniform atrophy of the epidermis and superficial dilated pilosebaceous follicle containing keratotic plugs and moderate perifollicular cellular infiltrate, as well as xanthoma cells in the lower left area ( $\times 75$ ). *B*, frozen section of tissue from younger lesion on left cheek showing changes similar to those in *A* and, in addition, patchy double refractile lipid deposit. Sudan III,  $\times 75$ .

vessels. A few areas of cellular infiltrate were observed in the upper portion of the subcutaneous fat.

Verhoeff's stains showed complete absence of elastic tissue in the xanthomatous infiltrate. In areas adjacent to the xanthomatous process there was some fragmentation of elastic tissue.

Tissue changes in the left malar region were essentially the same. Unfortunately, frozen sections used for

usually seen in xanthoma was not present. Lipids were not deposited in the cellular infiltrate which surrounded the dilated pilosebaceous follicles.

Polariscopic examination of stained frozen sections showed that the stained lipid infiltrate was doubly refractile. Where the deposit was less dense, double refractile crystals were observed. Therefore the lipid infiltrate contained cholesterol and cholesterol esters.

and confirmed the opinion that the process in this case was one of xanthosis.

To clarify further the type of xanthosis, photographs, sections of tissue from the original lesion and an abstract of the history were sent to Dr. Fred D. Weidman. Portions of his informal report are as follows:

From the histologic standpoint, there is only one feature that supports the diagnosis of lupus erythema-

large section like this. It is true that a few foci of lymphocytes can be discovered in the corium, but, again, they do not occur at all consistently throughout the section and are no more than might be expected in connection with the xanthomatous changes.

"As to the xanthomatous changes, they occur in a spotty way that suggests that they are occurring secondarily in some preexistent lesion. The presence of

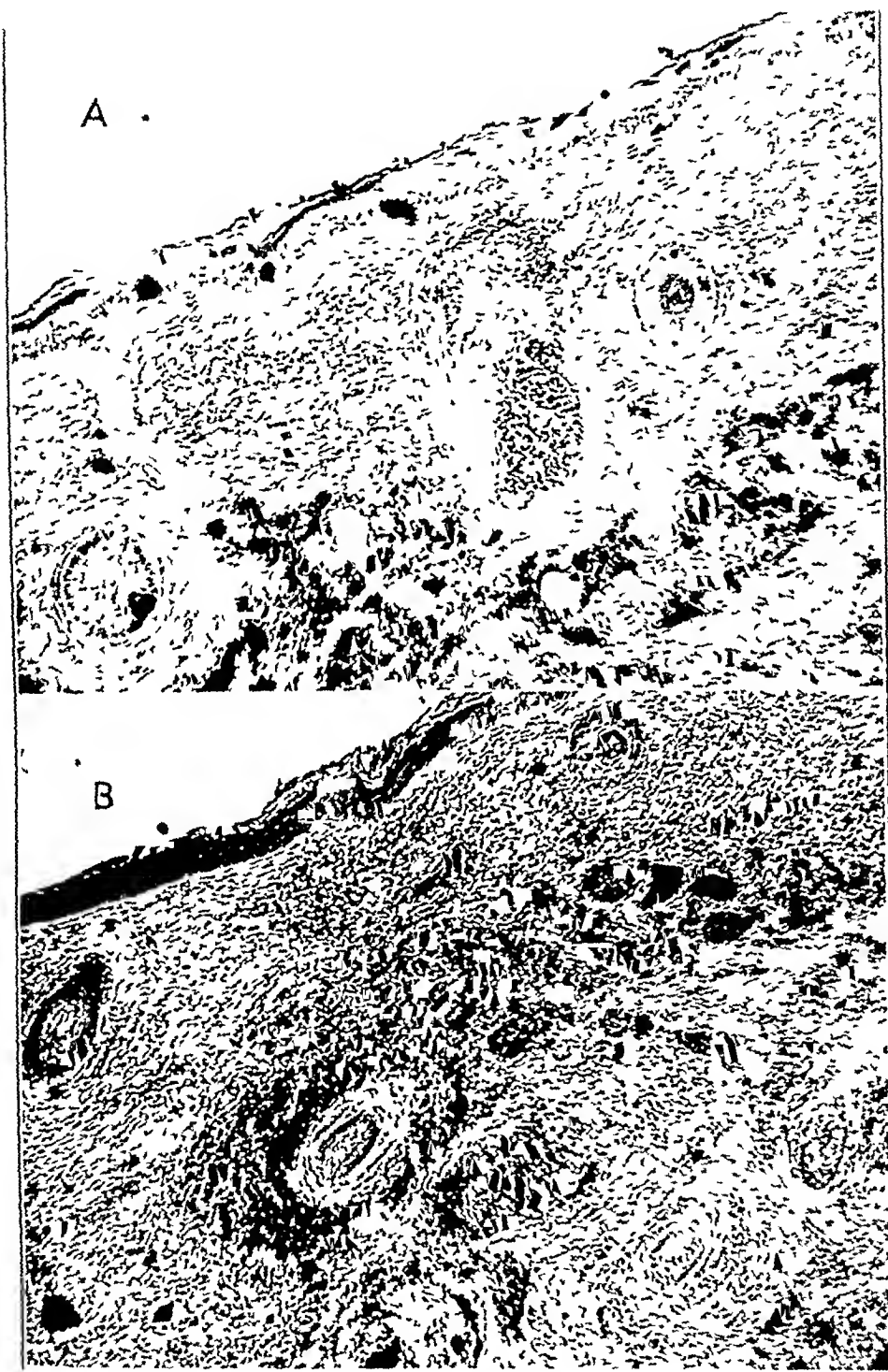


Fig. 3—Frozen sections from lesion in left malar region showing patchy intracellular and extracellular deposits of double refractile lipids. Note absence of lipid deposit in perifollicular infiltrate and in the more sclerotic areas. Sudan III,  $\times 75$ .

matosis, namely, the dilatation of the orifices of the hair follicles. This does not occur consistently, is never of high grade and does not extend at all deeply into the pilosebaceous follicle. The epidermis is atrophic in all its parts, whereas in lupus erythematosus one should expect to find some places where it was acanthotic, corresponding to some part of the lesion in which the changes were progressive. I cannot conceive that the cutaneous atrophy that occurs in lupus erythematosus would occur in such a uniform fashion throughout a

intervening regions of degeneration suggests that the xanthomatous changes are regressing.

"Under all those circumstances, though, I feel that the clinical features should overbalance the shortcomings of the histologic ones and that the case should be regarded as an instance of lupus erythematosus primarily. According to that, one has one more observation of xanthomatous changes superimposed on a well established dermatologic entity.

"I could not speak thus positively were not the photographs so excellent, with the pocket lens I could make out the follicular keratoses, in which connection it appears that the biopsy specimen, the scar of which can be plainly seen, did not pass through a region where the features of lupus erythematosus were more pronounced. This is one of the shortcomings of histologic studies, namely, that the pathologist is confined to study of a limited portion instead of the whole lesion."

xanthomas, to what group of the recognized xanthomatoses do they belong?

The symmetry and the butterfly distribution of the eruption are characteristic of discoid lupus erythematosus and not of any cutaneous xanthoma. The prolonged and relatively persistent erythema with slowly developing patchy xan-



Fig 4—A, focus of lymphocytic infiltration in corium ( $\times 100$ ) B, foamy cells seen throughout xanthomatous infiltrate (oil immersion)

#### COMMENT

This rare case is of special interest from the viewpoint of differential diagnosis and proper classification. Are the lesions primarily cutaneous xanthomas, or are they manifestations of a well established dermatosis with superimposed xanthomatous changes? If they are primarily

thomatous discoloration is not characteristic of xanthoma. Furthermore, the central scarring and dilatation of orifices of pilosebaceous follicles as well as follicular plugging strongly support the diagnosis of lupus erythematosus. The photosensitivity exhibited by the lesions is not uncommon in cases of lupus erythematosus and is not a characteristic of cutaneous xanthoma.



That this may be an unusual xanthoma planum similar to xanthoma palpebrarum is hardly tenable. Xanthelasma starts as flat yellow lesions, and the larger, more familiar xanthoma planum seen occasionally in xanthoma tuberosum does not possess the distinct patch type of xanthosis and follicular changes observed in this case.

Evidence from the clinical course and gross characteristics of the eruption favors a diagnosis of chronic discoid lupus erythematosus in which the xanthosis is a secondary process.

Histopathologic changes tend to support the clinical diagnosis but are not entirely confirmatory. The area from which the biopsy specimen was taken accounts for the variance between clinical and histopathologic observations. Even though follicular and perifollicular changes are not so great as those of uncomplicated lupus erythematosus, they cannot be ignored and are significant when correlated with the clinical features. The lipid infiltration is spotty or less diffuse than that of primary xanthoma. As pointed out by Dr. Weidman in his comment, this feature suggests that the xanthomatous changes were not of a primary nature.

For many years it has been thought that hepatic disease, particularly biliary cirrhosis, is in some way related to the pathogenesis of xanthoma. This point is emphasized in a number of the excellent communications of Weidman and his co-workers<sup>10</sup> and many others. Montgomery and Osterberg,<sup>11</sup> in a comprehensive correlation of the clinical, histopathologic and chemical studies of a large number of various types of cutaneous xanthoma, observed a high incidence of serious cardiovascular disease.

In the present case there was moderate essential hypertension and enlargement of the liver. The patient had never been jaundiced or had symptoms referable to her cardiac or hepatic disease. Unfortunately, I never had the opportunity of investigating this phase of her illness. In view of the present concept of xanthomatosis, hypertension and hepatic disease may have contributed to the pathogenesis of the scar xanthoma in this case. It should be recalled that the patient observed by Anderson had a serious cardiac disease.

An analysis of cases of scar xanthoma reviewed by Weidman and Boston<sup>4</sup> showed that in the majority of instances scar xanthoma occurred in patients who had cutaneous xan-

thoma of the generalized type or hypocholesteremia or both and that involved scars were young and those of common dermatologic entities. This suggests that scar xanthoma is more likely to occur in patients with generalized xanthomatosis and also that rarity of scar xanthoma in lesions of discoid lupus erythematosus may be due in part to the age of the scar and the infrequent coincidental occurrence of essential xanthomatosis and lupus erythematosus. In a series of 33 cases of lupus erythematosus, Jlnsky<sup>12</sup> found the average blood cholesterol level to be slightly above normal.

On the other hand, the experiments of Weidman<sup>2</sup> and clinical observations show that hypercholesteremia or the presence of essential xanthomatosis does not guarantee the development of xanthomatous changes in intercurrent scars caused by trauma or inflammatory disease. These observations emphasize the complexity of the pathogenesis of xanthomatous processes. For many years a similar confusion existed with regard to the significance of the presence or absence of hypercholesteremia in xanthoma tuberosum. Clarification of this point was achieved by clinical differentiation of xanthoma tuberosum from xanthoma disseminatum, however, nothing was added to the understanding of the causation or pathogenesis of xanthomatosis.

Thannhauser and Magendantz<sup>13</sup> have given a comprehensive summary of the present knowledge of the metabolism and function of cholesterol and have pointed out four possible disturbances in its intermediate metabolism which have been considered in the causation of essential xanthomatosis. There may be a diminished disintegration of cholesterol in the intermediate metabolism, a diminished excretion of cholesterol, a disturbed equilibrium between cholesterol and cholesterol esters or an increased synthesis of cholesterol. After considering these possible general disturbances of general cholesterol metabolism they concluded that there is no evidence to support the assumption that essential xanthomatosis is caused by a disturbance of intermediate cholesterol metabolism. They expressed the belief that the metabolic disturbance of cholesterol is localized in the xanthoma cells, which, according to Waldeyer and others, are embryonal cells which are able to form different

10 Weidman, F. D., and others. Xanthoma and Other Dyslipoides, Chicago, American Medical Association, 1941.

11 Montgomery, H., and Osterberg, A. E. Xanthomatosis. Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch Dermat & Syph **37** 373 (March) 1938.

12 Jlnsky, B. W. Ueber die Cholesterinämie bei Lupus erythematoses, Dermat Wchnschr **96** 739 (June 3) 1933, abstracted, Arch Dermat & Syph **28** 719 (Nov) 1933.

13 Thannhauser, S. J., and Magendantz, H. Different Clinical Groups of Xanthomatous Diseases. Clinical Physiological Study of Twenty-Two Cases, Ann Int Med **11** 1662 (March) 1938.



fats and to release the fats by degeneration. They concluded that essential xanthomatosis is a cellular metabolic disturbance caused by an embryonal metaplasia of certain cell groups and prefer to consider it a metaplastic reticular cholesterosis. They expressed the belief, however, that xanthoma cell formation may occur independently of essential xanthomatosis, thereby offering an explanation for the pathogenesis of localized xanthomatous change in certain tumors, cysts and scars.

The solution of the pathogenesis of lipidoses has been retarded chiefly because of the lack of comprehensive knowledge of the physiologic chemistry of general and cellular lipid metabolism.

#### SUMMARY AND CONCLUSIONS

A case of xanthomatous infiltration occurring in lesions of chronic lupus erythematosus was encountered. The diagnosis of discoid lupus erythematosus as the primary dermatosis is based chiefly on the clinical characteristics of the eruption, however, histopathologic changes were not entirely inconsistent with those observed in lupus erythematosus.

The xanthosis occurred in the scar of a pre-existent dermatologic entity, therefore it belongs to the scar xanthoma group of Weidman and Boston or resorption xanthelasma of Urbach.

"Scar xanthoma" is the preferable term. It satisfactorily describes the clinical manifestations of this unusual expression of xanthoma without an assumption relevant to its pathogenesis.

Factors responsible for the deposit of cholesterol and its esters in diseased tissue and the production of cellular changes appropriate for the development of xanthomatous infiltration are unknown. Suffice it to say that scar xanthoma does not involve old scars but, instead, occurs in tissue containing young, rapidly dividing reticular cells, some of which have undergone changes permitting abnormal cellular metabolism of cholesterol and related lipids.

#### ABSTRACT OF DISCUSSION

DR FRED D WEIDMAN, Philadelphia. I shall not have anything to say about the clinical diagnosis—that is, as to whether this case qualifies unequivocally as a case of lupus erythematosus. Assuming that this is correct, I shall discuss only the pathology.

First, what is the possible source of the lipids in cases in which there is no hypercholesteremia? In connection with a xanthosarcoma of the arm, I indicated (Weidman, F D. Xanthoma of the Cheek. *Succeeding Xanthosarcoma of the Forearm*, *Arch Surg* 34 792 [May] 1937) that stagnant, decomposing blood in situ might possibly be the source, blood being rich in cholesterol, both in the serum and in the red blood cells. I listed a number of highly vascular lesions which could become xanthomatous, such as hemangio-

mas. Dr Netherton's citation of Dr Bechet's case is another which adds weight to the thesis that blood which is in a state of stasis may predispose to local deposit of lipid. Too, in a case of what my colleague and I chose to call xanthoma pseudodiabeticorum (Weidman, F D, and Schaffer, H W. Xanthoma of the Skin and Larynx, *ARCH DERMAT & SYPH* 35 767 [May] 1937, and Weidman, F D. Position of "Pseudodiabetic Xanthoma" Among the Lipoid Disturbance of the Skin (Urbach), *ibid* 35 815 [May] 1937), there was lipid deposit in a larynx which contained evidence histologically of old hemorrhages. Accordingly, it may be that in this case of Dr Netherton's, it is the long-standing hyperemia which is a part of lupus erythematosus, with relative stasis, that determined the eventual deposition of the lipid substances.

A most significant lesson is to be learned from scar xanthomas with respect to classification. As I see it, the logical approach to this is through the clinical channels that Dr Netherton indicated in the lantern slides. In them, he showed a lengthy list of definitely established, well known clinical conditions, only after that did he consider the matter of classification on the basis of the chemistry, which, while highly important to the chemist, took second place.

To cite another example which bears on principles of classification. When we were discussing Dr Ketron's paper on erythema elevatum diutinum this morning, an alternative diagnosis of extracellular cholesterosis was advanced. It would be interesting to learn whether a reexamination of all the cases of extracellular cholesterosis would demonstrate that in them there is the histologic structure of erythema elevatum diutinum plus cholesterol. In other words, is extracellular cholesterosis simply erythema elevatum diutinum with the more or less fortuitous addition of a lipid phase? If so, I should be opposed to the acceptance of extracellular cholesterosis as a clinical entity. It should be "cholesterotic erythema elevatum diutinum" or "erythema elevatum diutinum with superimposed extracellular cholesterosis." This is in line with a contention that I have long held, namely, that in developing the classification of the lipidoses, one should not add more and more of them as entities simply because they exhibit this or that particular fatty feature. For example, Urbach's "imbibitio lipoidica collageni degenerativus" (Urbach, E. A Proposed Classification of Cutaneous Lipoidoses, *ARCH DERMAT & SYPH* 42 68 [July] 1940) is nothing more nor less than a dermatofibroma in which an excessive deposit of fatty substance has taken place, it is synonymous with the conventional dermatofibroma lenticulare. Incidentally, the hemosiderin deposits seen in that disease are doubtless an indication of previous hemorrhage, and the hemorrhage, in turn, may be the source of the locally deposited fats in that condition. Urbach's "imbibitio lipoidica tela elasticae degeneratae" is open to the same order of criticism. It appears to be synonymous with senile elastosis or sailor's skin. By no means should one interminably build up a complicated structure of new clinical lipid entities supplied from previously existing, well known, clinical dermatologic entities to which merely fat has been added.

To conclude with a final note concerning scar xanthomas, actual scars need not be seen in order to satisfy the criteria. Thus, the reactive pathologic processes need not proceed as far as fibrous tissue hyperplasia. Following erysipelas and eczema, lipidal substances may be added to the pathologic picture and give rise to xanthomatous appearances.

DR HAMILTON MONTGOMERY, Rochester, Minn I might add 1 other case to those of Dr Netherton, namely that of a patient which I reported (Montgomery, H Xanthomatosis Cutaneous Xanthoma, Especially in Relation to Disease of the Liver, *J Invest Dermat* 1 325-351 [Oct] 1938) as a probable instance of Burger-Grutz disease or of hepatosplenomegaly with cutaneous and mucous membrane lipidosis This patient had xanthelasma of the eyelids, xanthoma tuberosum on the elbows, xanthomatous deposits in the mucocutaneous surfaces of the mouth and hyperlipemia, especially an increase in phosphatides, but, in addition, had xanthomatous deposits in the laparotomy scar, the patient having had several operations

The possibility arises in Dr Netherton's case, in which there was enlargement of the liver even though there possibly was no hyperlipemia, that there may have been a generalized disturbance in cholesterol metabolism. It is known that xanthomatous lesions can occur secondary to hepatic disease In xanthoma disseminatum or disseminate types of xanthomatosis in which there is no hypercholesteremia or hyperlipemia, there still may be hepatic involvement A disturbance in lipid metabolism might explain, therefore, the xanthomatous deposits in an area of lupus erythematosus, the selection of this site resulting from a lowering of the normal resistance of the skin by the lupus erythematosus

DR NELSON PAUL ANDERSON, Los Angeles The question arises as to whether this is really a case of primary lupus erythematosus with secondary xanthomatous changes, as suggested by Dr Netherton, or whether the disease is primarily a xanthoma with changes which superficially resemble lupus erythematosus

If Dr Netherton's idea is correct, namely, that this is primarily lupus erythematosus with secondary xanthomatous changes, the question arises, why it is not encountered more frequently After all, lupus ery-

thematosus is not a particularly rare disease As suggested by Dr Netherton and Dr Montgomery, the idea has occurred that perhaps cases such as the present one are instances of lupus erythematosus occurring in persons with hepatic disease and that that particular group of patients tend to have secondary xanthomatous changes take place in their lesions of lupus erythematosus

I can add 2 cases to the group that has been mentioned 1 that has already been reported and 1 that was observed last February The clinical features appear to be striking The lesions are symmetric and occur particularly in the malar regions At first glance and at a distance they appear to be lupus erythematosus When one examines them closely, one sees a peculiar, yellowish tinge to them But after hearing Dr Netherton's excellent presentation I feel that he has reached the right conclusion, namely, that the disease is primarily lupus erythematosus with secondary xanthomatous changes

DR EARL W NETHERTON, Cleveland I am glad to have Dr Weidman emphasize, as he has done so very well in his writings, that this disease is xanthomatous involvement of scar tissue containing young fibroblasts This process is best designated by the term "scar xanthoma" rather than by that suggested by Urbach

As to the source of the lipids from hemorrhage or stagnant blood, Gross and Wolbach, as cited in the paper, in studying sclerosing hemangiomas pointed out that in some of their specimens they believed that the source of the lipid was interstitial hemorrhage They observed phagocytosis of lipids and hemosiderin in their sections The sclerosis was greatest in the capillary type of angioma, involving the skin, rather than in the vascular type, involving viscera It may be that stagnant blood or interstitial hemorrhage is a source of the lipids in some cases of scar xanthoma

# ALOPECIA CIRCUMSCRIPTA DUE TO VITAMIN A DEFICIENCY

## REPORT OF A CASE

S GILL, MD

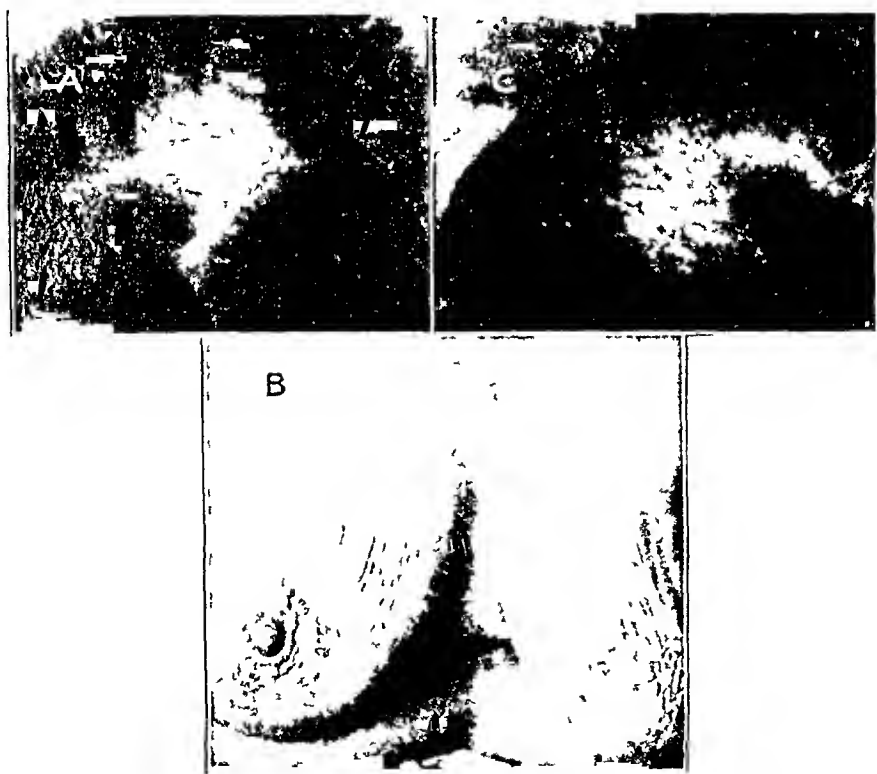
HAIFA, PALESTINE

A 40 year old woman of an Arab village was sent to me by the local physician for treatment of tinea capitis, a disease frequent in Palestine

Examining her scalp, I saw an isolated plaque with incomplete alopecia, 3 by 4 cm in extent, with irregular, ill defined limits. The area was covered with a mass of coarse adherent scales, elevated above the surface. There were no signs of inflammation. Hairs of various lengths protruded above the white mass. They had not lost their pigmentation. The shortest

The skin of the body was xerodermatic and rough, with symmetrically distributed areas covered with spinous papules. The mammary region, discolored to some degree, was covered with follicular and perifollicular hyperkeratotic masses.

Moderate itching had led to numerous excoriations. The palms and soles remained unchanged. The nails showed longitudinal ridges. The conjunctivas were unaffected, and there were no complaints of visual disturbances or night blindness. According to the



A, circumscribed patch of alopecia, B, follicular hyperkeratosis, C, return of hair after treatment with vitamin A

of them showed resistance to the epilating forceps while they were being removed for examination.

Microscopic examination of the hairs and scales after they had been soaked in 30 per cent solution of potassium hydroxide did not reveal mycelium or spores. A repeated microscopic examination after local applications of 5 per cent solution of dextrose during twenty-four hours showed the same picture.

The skin of the face was dry. The nose and the adjacent parts of the cheeks, the chin and the upper lip in some places were scaly, rough and harsh and partly depigmented and partly of a dirty slate color. The hyperkeratotic papules on the face were rather flat and contained no visible spines.

patient's statement, the changes on her skin had begun only some months previously. At the time of examination her complaints were increasing weakness and fatigue, abdominal pain and lack of appetite. Her diet showed a lack of nutritive essentials, as it consisted mostly of rice, legumes, mutton fat, bread and black coffee. She seldom ate vegetables and fruits and had a meat dish only about once a month, while milk, eggs and butter were rarities to her. Considering the typical cutaneous lesions and the deficient and faulty nourishment of the patient, it was not difficult to conclude that the dermatosis was due to vitamin A deficiency, though I had no opportunity to confirm it either through measurement of dark adaptation or through estimation of the vitamin A level of the blood.

I prescribed a daily ration of 4 glasses of milk, 3 eggs, half a glass of carrot juice, green vegetables in abundance, liver and butter and, in addition a daily dose of 30 drops of a vitamin A preparation containing 125,000 international units per gram and "diachylon salicylicum ointment" locally. The patient visited me again fourteen days later. I found that her general condition had improved enormously, the skin of her face was clean, and in the mammary region only traces of scaling were to be seen.

Only the spinous follicular elevations on various symmetric areas, especially on the back, had not yet disappeared entirely, although they were greatly diminished.

The plaque on the scalp was clean and covered with regularly growing hairs about 1 cm. long.

#### COMMENT

Taking into consideration the observations of Frazier and Hu, who saw atrophy of the hair bulbs and cystic degeneration in persons with avitaminosis A, and the observations of Sweet and K'ang, who found horny papules in the

pilosebaceous follicles,<sup>1</sup> one can assume a temporary alopecia caused by avitaminosis A as a direct sequel of such anatomic changes. The quick response of the hair follicles to vitamin A therapy can be compared with the usual quick disappearance of ocular lesions caused by vitamin A deficiency when the missing vitamin is given in abundance.

#### SUMMARY

A 40 year old woman in whom vitamin A deficiency had caused circumscribed alopecia and phrynoderma reported for treatment. Use of a diet rich in vitamin A and a preparation containing the concentrated vitamin during fourteen days cured the alopecia, almost completely cleared the skin and greatly improved the general condition.

1 Cited by Sutton, R. L., and Sutton, R. L., Jr. *Synopsis of Diseases of the Skin*, St. Louis, C. V. Mosby Company, 1942.

## HEPATOTOXIC ACTION OF ARSENICALS

EFFECT OF NEOARSPHENAMINE AND MAPHARSEN ON CHOLIC ACID SYNTHESIS  
AND USE OF DEHYDROCHOLIC ACID TO DIMINISH  
HEPATOTOXIC ACTION OF MAPHARSEN

J H ANNEGERS, MS, V A DRILL, PH D, J HABEGGER, BS,  
A C IVY, MD, AND A J ATKINSON, MD

CHICAGO

This investigation was undertaken to determine (a) whether the intravenous administration of neoarsphenamine and mapharsen affects the synthesis of cholic acid and, if so, (b) whether the oral administration of dehydrocholic acid for three days prior to and after the administration of the arsenicals will diminish the hepatotoxic action of these arsenicals.

This study was stimulated by the clinical report that the administration of sodium dehydrocholate ameliorates arsenical hepatitis.<sup>1</sup> In a previous study<sup>2</sup> we attempted to ascertain the physiologic rationale of the claim, and found that sodium dehydrocholate did not increase the excretion of the arsenicals in the bile. In fact, sodium dehydrocholate tended to decrease and sodium glycocholate and sodium taurocholate tended to increase the excretion of arsenic in the bile. These tendencies were not statistically significant and could have been due to chance or random sampling. However, an increased excretion of arsenic is only one mechanism by which bile acids may serve to oppose the hepatotoxic action of arsenicals. For example, sodium dehydrocholate may counteract their hepatotoxic action by increasing the hepatic arterial blood flow,<sup>3</sup> which may be presumed to favor reparative processes or to render the liver less vulnerable to toxic agents.

The synthesis of cholic acid was chosen as an indicator of the hepatotoxic action of the arsenicals because it is well known to be decreased

in the presence of hepatitis due to obstruction of bile ducts, infection or use of chloroform and to be reduced occasionally when drugs such as cinchophen and quinacrine hydrochloride are administered.<sup>4</sup>

We chose to administer preparations of dehydrocholic acid rather than sodium glycocholate and sodium taurocholate because the former do not significantly influence the synthesis or output of cholic acid in the bile.<sup>5</sup> Thus, should their administration prevent a depression of cholic acid synthesis due to mapharsen the results should be less equivocal than if a bile salt containing cholic acid such as sodium glycocholate were given.

### EXPERIMENTAL METHODS

Dogs with a permanent biliary fistula and a duodenal fistula for the return of bile were used. The surgical and experimental techniques were the same as previously described for yielding the most quantitative results,<sup>6</sup> except that the bile was collected in a bag without continuous suction. The dogs were fed an equal portion of the daily ration every twelve hours. Since the quantity and quality of food ingested are important in a study of cholic acid output, the food intake was carefully controlled, and results were not included if the animal refused to consume any portion of the daily ration or if diarrhea developed. Since the dogs vomited after receiving mapharsen, the injections were given ten hours after the last meal in order not to interfere with the consumption and digestion of the meal.

The bile was collected at the same time each day and assayed for cholic acid by the method of Reinhold and Wilson.<sup>7</sup>

This study was aided in part by a grant from the Clara L. Abbott Fund.

From the Department of Physiology, Northwestern University Medical School.

1 Appel, B. Sodium Dehydrocholate in Arsphenamine Poisoning, *Arch. Dermat. & Syph.* **27** 401 (March) 1933. Appel, B., and Jankelson, I. R. Treatment of Arsenical Hepatitis with Sodium Dehydrocholate, *ibid.* **32** 422 (Sept.) 1935.

2 Annegers, J. H., Snapp, F. E., Ivy, A. C., and Atkinson, A. J. The Effect of Bile Acids on the Biliary Excretion of Neoarsphenamine and Mapharsen, to be published.

3 Grodins, F. S., Osborne, S. L., Ivy, A. C., and Goldman, L. The Effect of Bile Acids on Hepatic Blood Flow, *Am. J. Physiol.* **132** 375, 1941.

4 Annegers, J. H., Snapp, F. E., Paskind, L., Ivy, A. C., and Atkinson, A. J. Retention of Atabrine in Animal Body. Excretion in Bile and Urine and Effect on Cholic Acid Output, *War Med.* **4** 176 (Aug.) 1943. Annegers, J. H., Snapp, F. E., Atkinson, A. J., and Ivy, A. C. Variations in Susceptibility to Cinchophen as Observed in Animals with Bile Fistulas, *J. Lab. & Clin. Med.* **28** 828, 1943.

5 Berman, A. L., Snapp, F. E., Ivy, A. C., Atkinson, A. J., and Hough, V. S. The Effect of Various Bile Acids on the Volume and Certain Constituents of Bile, *Am. J. Digest. Dis.* **7** 333, 1940.

6 Kocour, E., and Ivy, A. C. The Effect of Certain Foods on Bile Volume Output Recorded by a Quantitative Method, *Am. J. Physiol.* **122** 325, 1938.

7 Reinhold, J. G., and Wilson, D. W. Cholic Acid Determination, *J. Biol. Chem.* **96** 637, 1932.

When the effect of dehydrocholic acid was to be determined, the equivalent of 15 Gm of this substance was given in the form of either sodium dehydrocholate or a mixture of oxidized bile acids consisting chiefly of dehydrocholic acid<sup>8a</sup> at twelve hour intervals for three days before and after the administration of the arsenical

Neoarsphenamine was given intravenously in a single dose of 300 mg (60 mg of arsenic) and mapharsen in a single dose of 60 mg (17.4 mg of arsenic). Injection of an arsenical was not repeated more frequently than once a week. It was assumed that this was not too frequently because our previous study showed that arsenic disappeared from the bile within a week after the administration of such a dose.

The dose of mapharsen used, on the basis of body weight, is about twice the daily dose used in the intensive five day treatment of syphilis, the liver-body weight ratio being approximately the same in man and dog. A man weighing 70 Kg and receiving a daily dose of 240 mg obtains 3.4 mg per kilogram, a dog weighing 10 Kg and receiving a dose of 60 mg obtains 6 mg per kilogram. The L.D. 50 dose for dogs is 13 mg per kilogram. The dose used was chosen with the idea of obtaining evidence of a hepatotoxic action without endangering the life of the animals.

In order to prevent the possibility of the results' being altered by the development of an immunity to repeated injections of the arsenicals, the injections of neoarsphenamine and mapharsen with and without dehydrocholic acid were alternated between the different dogs.

# RESULTS

*The Effect of Neoarsphenamine on Bile Formation* Table 1 shows the results of 10 tests on 9 dogs in which the volume of bile and output of cholic acid, under the basal conditions of the

TABLE 1—Effect of 300 Mg of Neoarsphenamine on Bile Volume and Cholic Acid Output During Twenty-Four Hours After Injection of the Drug

Dog	Bile, Cc			Cholic Acid, Mg		
	Control	300 Mg Neoarsphenamine	Percentage Change	Control	300 Mg Neoarsphenamine	Percentage Change
O4	135	146	+ 8	1,379	955	—31
O7	129	127	0	1,944	1,313	—32
C7	129	181	+40	1,944	1,476	—24
D9	155	148	— 5	1,401	1,645	+17
F9	118	140	+19	1,433	1,690	+18
G5	150	162	+ 8	1,424	1,780	+25
G6	141	146	+ 3	1,285	1,446	+12
G9	134	141	+ 5	1,185	1,072	— 6
G10	89	84	— 6	853	816	— 4
H2	132	177	+34	1,097	982	—10
Average	131	145	+11	1,395	1,318	— 4

diet alone, without an injection of neoarsphenamine, are compared with the output after an injection.

The average control twenty-four hour volume output was 131 cc. The output during the first

<sup>8a</sup> The mixture of oxidized bile acids used was ketochol (G. D. Searle & Company).

twenty-four hours after the injection of 300 mg of neoarsphenamine was 145 cc. The average increase in the volume output of bile was 11 per cent. On the basis of our previous experience with the bile fistula dogs, when the bile is collected in a bag a plus or minus 10 per cent variation in a group of tests occurs spontaneously under basal conditions. So it cannot be con-

TABLE 2—Effect of 60 Mg of Mapharsen on Bile Volume and Cholic Acid Output During Twenty-Four Hours After Injection of the Drug

Dog	Bile, Cc			Cholic Acid, Mg			24 to 48 Hr After Mapharsen
	Control	After Mapharsen	Percentage Change	Control	After Mapharsen	Percentage Change	
G2	122	140	+15	1,752	1,232	—30	1,893
G3	217	227	+ 5	2,643*	2,133	—19	2,440
G5	150	145	— 3	1,425	552†	—61	913
G6	141	146	+ 3	1,285	830	—35	1,410
G6	120	116	0	1,152	267†	—77	530
G7	161	140	—13	1,902	1,428	—25	
G9	130	145	+11	1,105	915	—17	1,202
G10	98	87	—11	833	313†	—63	535
H2	143	171	+13	813	632†	—21	1,106
H3	131	156	+19	827	1,000	+17	1,286
Average	141	147	+ 4	1,384	940	—34	1,157
						—32	

$$\left[ \frac{1,384 - 940}{1,384} = -32 \right]$$

\* This is an unusually large synthesis for a 12 Kg dog.  
† These are definitely abnormal yields.

cluded that neoarsphenamine causes a choleresis. However, in 1 test on dog C 7 and in dog H 2 choleresis did occur.

The effect of the neoarsphenamine on synthesis of cholic acid was inconsistent. The average depression of 4 per cent is not significant. Since it is unusual for cholic acid synthesis to vary more than 25 per cent from day to day under basal conditions, we believe that the injection depressed cholic acid synthesis in 2 and possibly 3 tests, namely, in tests on dogs C 4 and C 7. In none of these tests was the output less than 800 mg. Previous experience has shown that hepatitis is present when the output is less than 800 mg in dogs receiving our standard diet.

## The Effect of Mapharsen on Bile Formation

Table 2 shows the results of 10 tests on 9 dogs. The injection of 60 mg of mapharsen produced no significant change in the volume output of bile. However the synthesis of cholic acid was decreased in 9 out of 10 tests. On the average, 34 per cent less cholic acid was synthesized during the twenty-four hour period after injection of mapharsen than in the three twenty-four hour periods before injection.



Ordinary methods of statistical analysis did not show a significant difference. This result was due chiefly to the unusually high rate of synthesis of dog G 3. However, the odds are only 10 in 1,024 in favor of 9 depressions occurring by chance in 10 tests. Moreover, our experience with many bile fistula dogs during the past eight years teaches that when our standard diet is fed any basal synthesis below 800 mg of cholic acid in dogs weighing 8 to 12 Kg establishes the presence of hepatitis. The fact that the cholic acid output increased again during the second and third days after the injection is additional evidence that the mapharsen was the cause of the depression.

*The Effect of the Oral Administration of Dehydrocholic Acid Before and After the Administration of Neoarsphenamine*—The results of 12 experiments on 12 dogs showed that dehydrocholic acid given orally before and after 300 mg of neoarsphenamine yielded no significant changes in cholic acid synthesis. This might be anticipated, since the neoarsphenamine alone failed to cause a significant depression except in 2 tests.

*The Effect of the Oral Administration of Dehydrocholic Acid Before and After the Administration of Mapharsen*—The results are shown in table 3, 10 tests were performed on 5 dogs.

TABLE 3—Effect of Feeding 15 Gm of Dehydrocholic Acid Every Twelve Hours Before and After Injection of 60 Mg of Mapharsen on Bile Volume and Cholic Acid Output During Twenty-Four Hours Following Injection of the Drug

Dog	Bile, Cc			Cholic Acid, Mg		
	Con trol	After Ma pharsen	Per centage Change	Con trol	After Ma pharsen	Per centage Change
G5	247	287	+16	1,380	1,050	-24
G5	260	238	- 8	1,040	520*	-50
G6	228	265	+16	1,075	1,130	+10
G6	216	225	+ 5	1,190	600*	-44
G7	202	324	+11	2,395	1,830	-21
G8	251	301	+20	1,107	997	-10
G9	232	289	+25	1,439	1,760	+22
G9	242	283	+17	1,580	1,130	-28
G10	205	281	+ 5	902	945	+ 5
G10	231	202	- 9	1,010	617*	-39
Average	246	275	+12	1,312	1,063	-18
						-19

$$\left\{ \begin{array}{l} 1,312 - 1,063 \\ 1,312 \end{array} \right. = -19\%$$

\* These are definitely abnormal yields

The average decrease in cholic acid synthesis in these tests was 18 per cent as compared with 34 per cent (table 2) when dehydrocholic acid was not administered. This difference appears to

show that the bile acid offered definite protection. However, it should be noted that 3 of the animals showed definitely abnormal cholic acid outputs, as compared with 4 of the animals which did not receive dehydrocholic acid, and the difference is not statistically significant.

COMMENT

It is generally recognized that in animals mapharsen is about twelve times as toxic on the basis of weight as neoarsphenamine. Thus it is not surprising that we found 60 mg of mapharsen to be more toxic to the liver, as judged by cholic acid synthesis, than 300 mg of neoarsphenamine. If we had used a dose of 720 mg of neoarsphenamine (12 × 60 mg), it is likely, in view of the fact that 300 mg caused evidence of hepatic damage in 2 of 9 dogs, that most dogs would have manifested temporary hepatic damage, as occurred with 60 mg of mapharsen.

On the contrary, recent clinical literature indicates that neoarsphenamine is more hepatotoxic than the foregoing figures indicate. For example, Leifer, Chargin and Hyman<sup>8</sup> observed 382 patients with syphilis treated with 800 mg of neoarsphenamine daily for five days and 240 mg of mapharsen daily for five days. Jaundice occurred in 3.6 per cent of the patients given neoarsphenamine and in 0.7 per cent of those receiving mapharsen. Peripheral neuritis was also more frequent when neoarsphenamine was given. Sadusk and associates<sup>9</sup> gave the same dose of mapharsen to 33 patients for five days and observed no change in the icteric index and sulfobromophthalein clearance. And Levin and Keddie<sup>10</sup> found transitory jaundice to have been reported in only 0.2 per cent of 10,370 patients who had received various doses of mapharsen. Either the differences observed by Leifer and co-workers are fortuitous, or the results of toxicity studies on animals are not applicable to man, or the rate of excretion of the two arsenicals by the liver is the determining factor.

The rate of excretion is an important factor determining the toxicity of drugs. In a previous

8 Leifer, W., Chargin, L., and Hyman, H. T. Massive Dose Arsenotherapy in Early Syphilis by Intravenous Drip Method, J A M A 117 1154 (Oct 4) 1941.

9 Sadusk, J. F., Craig, B., Brookens, N., Poole, A. K., and Strauss, M. J. Observations on Massive Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method, Yale J Biol & Med 14 333, 1942.

10 Levin, E. A., and Keddie, F. Toxic Effects Following the Use of Mapharsen, J A M A 118 368 (Jan 31) 1942.

study<sup>2</sup> it was found that 40 per cent of the arsenic in mapharsen was excreted by the liver in forty-eight hours whereas seventy-two hours was required for the excretion of 40 per cent of the arsenic in neoarsphenamine when single doses of the drugs were given. Hence, when the two arsenicals are given intensively, it is probable that neoarsphenamine accumulates in the liver to a greater extent than mapharsen.

It should be reiterated that the depression of cholic acid synthesis caused by the injection of mapharsen was transitory and the rate of synthesis returned to normal not later than the third day after the drug was given (table 2).

The results of the oral administration of preparations of dehydrocholic acid were unfortunately indecisive. The depression of cholic acid synthesis was not reduced consistently or entirely prevented (compare table 2 with table 3).

Even though dehydrocholic acid appeared to offer some protection of the liver from the hepatotoxic action of mapharsen when the results were compared with those for a control series deprived entirely of salts, it does not follow that an intact animal in which bile acids normally circulate will be similarly benefited by additional bile acids. If a more significant difference between the series with and without bile acid had occurred, further study would have been indicated.

We suspect that therapeutic doses of the arsenicals produce evident hepatic damage clinically only in patients with a reduced margin of safety in the liver. And it is possible that a disturbance of the liver predisposes to arsenical encephalopathy. Thus, it is our opinion that the hepatic function should be studied prior to intensive arsenotherapy and that all patients prior to

receiving arsenotherapy should be given a diet which is known experimentally to affect favorably the resistance of the liver to poisons.<sup>11</sup> In regard to administration of bile salts, it would appear that if the diet contains adequate protein flow of bile should be adequate and the administration of a bile acid would be superfluous, unless the increased hepatic arterial flow may have a desirable effect. To provide insurance against the possible presence of diminished bile formation due to the depressing influence of a high carbohydrate intake or to the presence of extremely viscous bile in some of the smaller biliary ducts, the use of bile salts is indicated. Otherwise, there is no clear rationale known for the use of bile salts in arsenotherapy.

#### CONCLUSION

A dose of 300 mg of neoarsphenamine does not consistently depress cholic acid output in dogs with a permanent biliary fistula.

Mapharsen in a dose of 60 mg consistently depresses cholic acid output in biliary fistula dogs deprived of bile acids.

Oral administration of dehydrocholic acid may aid in counteracting the hepatotoxic action of mapharsen.

It is suggested that patients scheduled to receive intensive arsenotherapy should have the function of their liver examined by one of the more sensitive tests (e g, the 5 mg sulfobromophthalein test) and be given a diet known to affect favorably the resistance to poisons for two or three days prior to the initiation of the therapy.

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11 Ivy, A. C. The Rationale of Therapy in Hepatic Disease, *Quart Bull, Northwestern Univ M School* 16 1, 1942.

# DETERMINATION OF MACROCYTIC ANEMIA AS AN AID IN DIAGNOSIS OF CERTAIN DEFICIENCY DERMATOSES

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WITH THE TECHNICAL ASSISTANCE OF LUCILLE LIVENHAL

ST LOUIS

In man, nutritional deficiencies of the various fractions of the B complex except thiamine are usually multiple, one or two symptoms are frequently present long before a fully developed disease syndrome makes its appearance. Examples of this limited effect are seen in cheilosis, greasy desquamation of the nasolabial folds, vascularization of the cornea which occurs in ariboflavinosis,<sup>1</sup> stomatitis, gastritis, dermatitis, diarrhea and constipation which often occur singly in niacin deficiency<sup>2</sup> and the nonpellagrous dermatoses such as those reported by Gross.<sup>3</sup>

In the experimental animal, changes involving the various tissues may be produced at will by withholding one or more of the various fractions of the B complex. These changes may be produced in the gastrointestinal tract, the nervous system, the hemopoietic system and the skin.

There are only two fractions of the B complex, niacin and riboflavin, which are known to affect cutaneous changes in man. All other dermatoses resulting from the absence of this essential com-

ponent of the diet must be the effect of the lack of the unidentified fractions or of biotin or folic acid and others which at this time have not been sufficiently investigated.

Castle,<sup>4</sup> Harris<sup>5</sup> and others have pointed to the close similarity between the known deficiency diseases, pernicious anemia, pellagra and sprue. The major symptoms in each are different, yet in each there are often found identical symptoms. In pellagra, which differs from pernicious anemia and sprue by the constant involvement of the skin, macrocytic anemia is often encountered.

Ruffin and Smith<sup>6</sup> and Spies<sup>7</sup> have reported on the beneficial effect of liver extract on the gastrointestinal symptoms and anemia of pellagra. Goldsmith<sup>8</sup> has observed patients with chronic nutritional deficiency but without the clinical picture of pellagra who showed a severe macrocytic anemia and who responded to liver extract.

Hematologic studies were made on 179 patients with various dermatoses (table 1). The hematocrit value, the mean corpuscular volume and the mean corpuscular hemoglobin concentration indexes were determined according to the

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2 Aykroyd, W R, Krishnan, B G, and Passmore, R. Stomatitis of Dietary Origin (Treated by Nicotinic Acid), *Lancet* **2** 825-828 (Oct 14) 1939. Martin, G J, Thompson, M R, and de Carvajal-Forero, J. Influence of Single and Multiple B Complex Deficiencies upon Motility of Gastrointestinal Tract, *Am J Digest Dis* **9** 268-273 (Aug) 1942. Strauss, M B. Role of Gastrointestinal Tract in Conditioning Deficiency Disease. Significance of Digestion and Absorption in Pernicious Anemia, Pellagra and "Alcoholic" and Other Forms of Polyneuritis, *J A M A* **103** 1-4 (July 7) 1934.

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6 Ruffin, J M, and Smith, D T. Treatment of Pellagra with Certain Preparations of Liver, *Am J M Sc* **187** 512-521 (April) 1934.

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8 Goldsmith, G A. Personal communication to the author.

method of Wintrobe<sup>9</sup> Repeated examinations were done, when possible, on those patients showing wide variations from normal and those for whom a clinical diagnosis of deficiency dermatitis was made As treatment progressed, additional examinations of the blood were performed

TABLE 1—Incidence of Macrocytic Anemia in Patients with Various Dermatoses

Disease	Total No of Patients	With Macrocytic Anemia Number	Per Cent
Erythematous dermatitis of head, neck and shoulders	11	10	91
Nonpellagrous eruptions of wide distribution	31	16	52.3
Ariboflavinosis	11	1	9.1
Photosensitization	4	0	0
All other dermatoses	122	29	23.8

There were 42 patients who complained of cutaneous lesions which did not conform to any dermatologic entity For 31 of these a diagnosis of dermatitis resulting from deficiency was made on the basis of the objective cutaneous symptoms in addition to the presence of changes in the mucosa of the mouth, the existence of constipation or diarrhea, evidence of xeroderma, follicular keratotic plugging, brittle nails, keratosis of the conjunctiva, fissures of the oral commissures and a history of inadequate diet In no instance was a diagnosis of pellagra supported by the results of examinations

Fifty-two per cent of this group were found to have an increase in the mean corpuscular volume These patients responded at once to proper dietary measures and parenteral injection

TABLE 2—Hematologic and Clinical Observations at Time of Diagnosis

Case	Sex	Age	Red Blood Cells	Hb (Sahlb) Gm	MCV	MCHC	Dermatitis
1	F	37	3.8	11	110	26	Neck, face
2	F	48	3.5	13	142	25	Neck, face, hands
3	F	48	4.3	14	102	31	Neck, face
4	M	60	4.5	13	132	21	Neck, arms, legs
5	F	58	3.2	13.5	131	32	Neck, face, ears
6	F	53	5	13	109	28	Neck, face
7	F	59	4.1	12.5	112	27	Neck, face, hand
8	F	50	4.4	13	105	28	Neck, axillary folds
9	F	45	3.6	12.5	113	30	Neck, arms
10	F	57	4.7	14.5	110	28	Neck, ankle
11	F	39	4.2	12	84	33	Neck, axillary folds

tions of liver extract The finding of macrocytic anemia in this group was an aid in establishing a diagnosis for slightly over one half The con-

ditions observed on physical examination and the dermatologic evaluation of the patient were the most important factors Liver therapy was effective in bringing about a clinical cure in each instance The mean corpuscular volume in all cases returned to normal

There were 11 patients who presented similar cutaneous lesions, 91 per cent of whom had macrocytic anemia (table 2) Response to parenteral injection of crude liver extract produced immediate improvement in the symptoms of pruritus and dermatitis and an early return in the size of the erythrocytes to normal (table 3) One patient whose dermatitis proved resistant ultimately yielded to continuous injections of crude liver extract (case 7) In case 8 the cutaneous symptoms failed to respond to crude liver extract, pyridoxine, calcium pantothenate and whole vitamin B complex administered parenterally as well as dilute hydrochloric acid, a

TABLE 3—Hematologic and Clinical Observations Following Parenteral Injections of Crude Liver Extract

Case	Sex	Age	Red Blood Cells	Hb (Sahlb) Gm	MCV	MCHC	Dermatitis
1	F	37	4.6	13.5	95	30	Clear
2	F	48	4.9	14.5	96	30	Clear
3	F	48	4.9	13	91	28	Clear
4	M	60	4.9	13.5	94	29	Clear
5	F	58	4.6	13.5	95	29	Clear
6	F	53	4.1	13	89	33	Clear
7	F	59	5.2	12	84	27	Improved
8	F	50	5.3	13.5	74	34	Improved
9	F	45	4.5	11.5	83	30	Clear
10	F	57	5.4	15.5	87	32	Clear

high vitamin diet and massive doses of all vitamins administered by mouth The blood picture changed from that of a macrocytic anemia to that of a simple microcytic type

These observations indicate that a clinical syndrome consisting of dermatitis and macrocytic anemia, resulting from a deficiency of fractions of the B complex present in liver extract, exists

The cutaneous lesions in the early stages consisted of evanescent, patchy or diffuse, superficial, pruritic, scaly, dry or vesicular erythroderma In the later stages the patches, which lost their evanescent character, became confluent and the vesiculation tended to disappear The skin became edematous and slightly thickened

In all cases the lesions were distributed on the sides of the neck, the face, the anterior part of the shoulders, the upper part of the chest and the areas immediately adjacent to the anterior axillary folds Five patients presented lesions of similar character on the extremities There was an imperfect symmetry of the lesions, one side usually being more involved than the other The patients complained of intense itching

9 Wintrobe, M. M. The Volume and Hemoglobin Content of the Red Blood Corpuscle. Simple Method of Calculation, Normal Findings and Value of Such Calculations in the Anemias, *Am J M Sc* **177**:513-523 (April) 1929

The series is composed of 10 women and 1 man. All came from the middle or upper economic levels. All declared that they ate an ample amount of food or enough to satisfy the appetite. Specific questioning invariably revealed poor dietary habits and inadequate consumption of food. Two patients were thin and underweight, 1 was greatly overweight, and in the others the weight was normal. All complained of mild mental depression, apprehension and fatigue. One patient was first seen in a ward for patients with mental disease. The others had been able to carry on their usual duties. The ages varied from 35 to 60.

All patients had been under the care of other physicians, and most of them were taking some form of vitamin therapy by mouth. One patient (case 1) had experienced fissures of the commissures of the mouth at the time of the onset of the dermatitis. Riboflavin, which had been prescribed by her family physician, produced an immediate healing of the oral lesions without altering the pruritic erythroderma of the neck. There was a tendency to spontaneous remissions and recurrences in cases 1, 2, 4, 5, 6 and 8.

A general xeroderma was present in 2 cases. Except for the presence of hyperglycemia in 1 instance, there were no evidences of metabolic disease. Symptoms referable to the gastrointestinal tract, except loss of appetite, were not found. Koilonychia was present in case 4.

In 10 cases the study of the blood revealed a mild reduction of the erythrocytes, and increase in the mean corpuscular volume and a decrease in the mean corpuscular hemoglobin concentration (table 2). The leukocytes for the most part were found to be in the lower range or below normal. In 1 case in which typical clinical symptoms of the skin were presented there was a normal blood picture (case 11).

Gastric analysis was possible in 2 cases, and each revealed an absence of free hydrochloric acid and low total acidity.

#### REPORT OF CASES

**CASE 1**—J. A., a woman aged 37, a teacher, consulted me on April 5, 1943, complaining of a dermatitis and severe itching of the cheeks, neck, eyebrows and eyelids. The disease had its onset in December 1942 as a patchy dermatitis of the neck and fissures of the commissures of the mouth.

Riboflavin, which she had taken in adequate doses for five months, produced healing of the commissural lesions but had no effect on the dermatitis of the face and neck. Since the onset two spontaneous remissions of the dermatitis had occurred, each followed by an attack of greater intensity.

The patient's general health had been good. Her weight had increased slowly over a period of years.

She considered herself to be in good health. She had had no abnormal gastrointestinal symptoms. Her menses were normal. She said that she had a good appetite, but on inquiry as to the specific foods, it was found that the total diet was unbalanced and inadequate, consisting of one full meal a day. The past history was noncontributory, except for an appendectomy which was performed in 1938.

Dermatologic examination of the patient revealed superficial, erythematous, vesicular, pruritic patches of dermatitis varying from 1 to 4 or 5 cm in diameter on the sides of the neck and on the cheeks, supraorbital area and eyelids. The mucosa of the mouth was pale. Bitot spots were present in both eyes.

Because of the character of the lesions at the time of the original examination, a diagnosis of contact dermatitis was made. Use of all cosmetics, including finger nail lacquer, also soap and soap powders, was stopped. At the end of ten days, no improvement had occurred.

Laboratory examination of the blood on April 16, 1943 revealed the following values: white blood cell count 5,834, red blood cell count 3,867,000, hemoglobin content (Sahli method) 11 Gm, mean corpuscular volume 110 cubic microns, mean corpuscular hemoglobin 28 micrograms and mean corpuscular hemoglobin concentration 26 per cent. The color index was 0.85, saturation index 0.75 and volume index 1.2. A differential count was within normal limits. The blood smear showed anisocytosis with the predominance of microcytes, poikilocytes and hypochromasia. The basal metabolic rate was -11 per cent.

Because of the history of an inadequate diet, a low hemoglobin content and an increased mean corpuscular volume, the patient was given a balanced diet, dilute hydrochloric acid by mouth, 150,000 U. S. P. units of vitamin A daily and ferrous sulfate by mouth. In addition, 3 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly.

The subjective symptoms of itching disappeared promptly, and the lesions began to fade immediately. Examination of the blood which was made five weeks after treatment had been administered revealed normal values. When the patient was seen for the last time, on May 29, 1943, she was free of all evidence of disease. One year later there had been no recurrence.

**CASE 2**—O. M., a 48 year old housewife, consulted me for the first time in July 1940, with an acute vesicular dermatitis of the backs of the hands. A tentative diagnosis of contact dermatitis was made. The condition cleared quickly under soothing applications. A recurrence in January 1941 responded to the same treatment.

The third attack occurred in October 1941, as an acute vesicular dermatitis of the hands, arms, neck and nasolabial folds. Fissures were present in the commissures of the mouth. The tongue was smooth and livid. The history, which was otherwise unimportant, revealed a prolonged period of inadequate diet. The chief complaint was intense itching of the involved areas.

Laboratory examination of the blood in October 1941 revealed the following values: white blood cell count 6,834, red blood cell count 3,520,500, hemoglobin content (Sahli method) 13 Gm, mean corpuscular volume 142 cubic microns, mean corpuscular hemoglobin 37 micrograms and mean corpuscular hemoglobin concentration 25 per cent. The color index was 1, saturation index 0.8 and volume index 1.5. A differential count was within normal limits. The blood smear showed macrocytosis and poikilocytosis.

Because of the history of an inadequate diet and the hematologic values, the patient was placed on a balanced diet and orally she was given vitamin B complex (concentrated extract of liver and yeast, containing thiamine) with liver capsules (concentrated extract of beef liver and the anti-pernicious-anemia factor with ferrous sulfate), 150,000 U S P units of vitamin A daily and 9 mg of riboflavin daily. In addition, 3 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly for a period of three months.

There was improvement generally, with healing of the fissures in the commissures of the mouth. Examination of the blood which was made three months after therapy had been instituted revealed all values within the normal range. The patient discontinued treatment.

In August 1943, two years later, the patient consulted me for the fourth time, complaining of a recurrence of the lesions of the skin of the backs of the hands and fissures in the commissures of the mouth. The tongue was red, slick and fissured. Examination of the blood at that time revealed the following values: red blood cell count 3,762,500, hemoglobin content (Sahli method) 11.5 Gm, mean corpuscular volume 110 cubic microns, mean corpuscular hemoglobin 31 micromicrograms and mean corpuscular hemoglobin concentration 28 per cent. The color index was 0.9, saturation index 0.8 and volume index 1.2. The blood smear showed anisocytosis and poikilocytosis.

The patient was placed under treatment but disappeared from my observation.

CASE 3—T F, a woman aged 48, a housewife, consulted me in July 1941, complaining of a pruritic dermatitis of the face, neck and eyelids which had been present for one month. A tentative diagnosis of contact dermatitis was made, and the patient was instructed to discontinue use of all cosmetics, soap and soap powder. At the end of two weeks no improvement had occurred. On further questioning, the patient stated that she had been on a reducing diet. She also gave a history of the dermatitis becoming worse after exposure to the sun. The menses had stopped normally four years before. The patient complained of constipation. The past history was essentially noncontributory.

Dermatologic examination revealed an erythematous, superficial, vesicular, diffuse dermatitis which was present on the eyelids, nose, chin, cheeks and neck. The nails were pale and splitting. The tongue was pale. The rest of the body was free of dermatitis.

Laboratory examination of the blood in July 1941 revealed the following values: white blood cell count 6,032, red blood cell count 4,370,500, hemoglobin content (Sahli method) 14 Gm, mean corpuscular volume 102 cubic microns, mean corpuscular hemoglobin 34 micromicrograms and mean corpuscular hemoglobin concentration 31 per cent. The color index was 0.95, saturation index 0.93 and volume index 1.1. A differential count was within normal limits. The blood smear showed macrocytosis. The basal metabolic rate was +5 per cent. The urine was normal.

As the result of the condition of the blood and the history of an inadequate diet, the patient was placed on a balanced diet, and vitamin A, 150,000 U S P units daily by mouth, and parenterally 3 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter, was given twice weekly.

Treatment was continued for a period of two months, after which time the cutaneous lesions had healed. The hematologic values at that time were within normal limits.

CASE 4—M J, a 60 year old salesman, consulted me in February 1941 regarding an intensely pruritic dermatitis of the right ankle, toes, legs, scrotum, perineum, arms and neck. With local therapy, the lesions improved.

In October of the same year, the patient returned with a recurrence of the dermatitis. Examination revealed a widespread erythroderma, involving the neck, arms, legs, ankles, scrotum and perineum. He complained of intense itching. The rest of the body was free of lesions except for the presence of spooning of the finger nails. There also was noted a general though vague depression and anxiety. The patient was very thin.

Laboratory examination of the blood in October 1941 revealed the following values: white blood cell count 5,824, red blood cell count 4,504,000, hemoglobin content (Sahli method) 13 Gm, mean corpuscular volume 132 cubic microns, mean corpuscular hemoglobin 28 micromicrograms, mean corpuscular hemoglobin concentration 21 per cent. The color index was 0.84, saturation index 0.74 and volume index 1.3. The differential count was within normal limits. The blood smear showed poikilocytosis, hypochromasia and anisocytosis with predominance of macrocytes. The urinalysis revealed essentially normal values.

Because of the history and the hematologic values, the patient was given liver and iron capsules by mouth, also dilute hydrochloric acid and later B complex with liver. He was placed on a well balanced diet and given intramuscularly 2 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter two or three times a week.

Under treatment the patient gained in weight, his dermatitis disappeared and his general well-being was improved. After six weeks of intensive treatment, the hematologic values were within normal limits.

CASE 5—H P, a 58 year old housewife, consulted me in August 1942, complaining of an itchy dermatitis of the ears, occipital region and perianal region which had been present for six months. The general health had been good except for constant worry and nervous tension. She had a clinical recovery with local applications, sedatives and roentgen ray treatments.

In April 1943 she returned with an acute dermatitis of the face, neck, scalp, ears and eyelids accompanied by intense itching. She gave a history of poor appetite and eating sporadically.

Laboratory examination of the blood in April 1943 revealed the following values: white blood cell count 9,550, red blood cell count 3,290,000, hemoglobin content (Sahli method) 13.5 Gm, mean corpuscular volume 131 cubic microns, mean corpuscular hemoglobin 42 micromicrograms and mean corpuscular hemoglobin concentration 32 per cent. The color index was 1.2, saturation index 1 and volume index 1.4. The differential count was within normal limits. The Kahn reaction of the blood was negative. The urine was normal.

The patient was given liver and yeast extract by mouth, also riboflavin, dilute hydrochloric acid and vitamin A, 150,000 U S P units per day. She was placed on a balanced diet. Intramuscularly, she was given 2.5 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter every two days.

In January 1944 the hematologic values were within normal range and the patient had improved generally and there were no objective symptoms. She had one slight recurrence of the dermatitis which cleared with injections of liver extract.

CASE 6—C G, a woman aged 53, a seamstress, consulted me in November 1943, complaining of a pruritic, erythematous dermatitis of the chin, cheeks, sides and



anterior surface of the neck and upper pectoral area of the chest which had been present for six weeks. She gave a history of having had a "nervous stomach" for years, an insufficient diet, lack of appetite, nausea and diarrhea, loss of weight and periods of moderately severe mental depression. She was pallid. The past history was noncontributory except for a nervous breakdown which she had had five years prior to the present illness.

The cutaneous eruption consisted of superficial patches of erythematous dermatitis, some of which were covered with a fine desquamation. The size of the patches varied from 0.5 to 3 or 4 cm in diameter. The edges were not sharply defined.

The laboratory examination of the blood in November 1943 revealed the following values: red blood cell count 5,040,000, hemoglobin content (Sahli method) 13 Gm, mean corpuscular volume 109 cubic microns, mean corpuscular hemoglobin 26.4 micromicrograms and mean corpuscular hemoglobin concentration 28.6 per cent. The color index was 0.76, saturation index 0.89 and volume index 1.

The patient was placed on a well balanced diet, and 3 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter was given parenterally twice weekly. In December 1943, after one month's treatment, the dermatitis had cleared. The hematologic values at that time were within normal limits, with the exception of a slight reduction in the red blood cell count. The injections of liver extract were discontinued, but the patient was instructed to take liver extract by mouth. She admitted an improvement in her general feeling of well-being.

The patient remained well until March 1944, when she suffered a recurrence of the dermatitis on the sides of the neck and face. She stated that she had become emotionally upset, had lost her appetite and had been nauseated for the past two months. She had continued taking the liver extract by mouth.

Examination of the blood at this time showed the following values: red blood cell count 3,990,000, hemoglobin content (Sahli method) 13 Gm, mean corpuscular volume 103 cubic microns, mean corpuscular hemoglobin 32 micromicrograms and mean corpuscular hemoglobin concentration 31 per cent. A gastric analysis made at this time showed no free hydrochloric acid and a total acid of 6 per cent.

Parenteral injections of liver and dilute hydrochloric acid by mouth produced a rapid return of all signs to normal.

**CASE 7**—R. U., a woman aged 59, a delicatessen operator, consulted me in January 1944, complaining of an itchy dermatitis of the sides of the neck which had had its onset in October 1943. She said that there had been three partial remissions of the dermatitis after the onset. She had a fair appetite but was too busy to eat. Her general health had been good. She complained of constipation.

Examination of the skin revealed an erythematous, squamous, pruritic dermatitis of the sides of the neck, on the chest (fig. 1), about the lips, on the chin and on the right hand and wrist. The tongue was gray and spotted.

Examination of the blood showed the following values: white blood cell count 7,650, red blood cell count 4,162,500, hemoglobin content (Sahli method) 12.5 Gm, mean corpuscular volume 112 cubic microns, mean corpuscular hemoglobin 30 micromicrograms and mean corpuscular hemoglobin concentration 27 per cent. The color index was 0.89, saturation index 0.86 and volume index 1.2. The differential count was within

normal limits. The blood smear showed anisocytosis, with macrocytes predominant and poikilocytes. The Kalin reaction of the blood was negative.

The patient was placed on a well balanced diet and was given dilute hydrochloric acid by mouth. In addition, 3 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter was given parenterally twice a week. Later the patient was given B complex, nikethamide, calcium pantothenate and nicotinamide combined with the crude liver extract parenterally, without accelerating the clinical progress.

After five weeks of treatment, the blood count revealed the following values: red blood cell count 5,233,500, hemoglobin content (Sahli method) 12 Gm, mean corpuscular volume 84 cubic microns, mean corpuscular hemoglobin 23 cubic micromicrograms and mean corpuscular hemoglobin concentration 27 per cent. The color index was 0.67, saturation index 0.89 and volume



Fig. 1 (case 7)—Diffuse squamous dermatitis of the neck and chest.

index 1. The cutaneous lesions showed improvement, all areas were fading, and the patient had gained in weight, was less tired and felt more ambitious. Under continuous administration of crude liver extract, the skin returned to normal.

**CASE 8**—K. D., a woman aged 50, a stenographer, consulted me in October 1941, complaining of a pruritic dermatitis of the lips, eyelids and left side of the neck. A diagnosis of contact dermatitis was made at this time. With roentgen ray treatments and stopping use of cosmetics, the dermatitis disappeared. In January 1942 she had a recurrence of the dermatitis on the sides of the neck, which responded to local therapy and removal of cosmetics. In October 1943 she had a recurrence of the dermatitis for the third time, which failed to respond to treatment. At this time the lesions resembled neurodermatitis, and the patient was given mild sedatives.

In January 1944 a diagnosis of deficiency disease was made. Examination of the cutaneous lesions at that time revealed a patchy superficial erythematous, squamous, dry pruritic dermatitis of the sides of the neck, over the pectoral area and in the anterior axillary folds. Fissures were present in the commissures of the

mouth The patient gave a history of dieting to reduce weight

Examination of the blood in January 1944 revealed the following values white blood cell count 6,816, red blood cell count 4,442,500, hemoglobin content (Sahli method) 13 Gm, mean corpuscular volume 105 cubic microns, mean corpuscular hemoglobin 29 micromicrograms and mean corpuscular hemoglobin concentration 28 per cent The color index was 0.86, saturation index 0.89 and volume index 1.1 The differential count was within normal limits The blood smear showed macrocytosis and poikilocytosis Gastric analysis showed no free hydrochloric acid

The patient was given a well balanced diet, liver extract and dilute hydrochloric acid by mouth and parenterally crude liver extract containing 2 hemopoietic units per cubic centimeter, the dose starting at 1 cc and being increased to 4 cc per injection, twice weekly In conjunction with the crude liver extract, calcium pantothenate and nicotinamide were also administered

Examination of the blood after two months of treatment with parenteral injections of liver extract revealed a decrease in the mean corpuscular volume from 105 to 74 cubic microns At the same time the mean corpuscular hemoglobin concentration increased from 28 to 34 per cent This shift in the blood picture indicated that the anemia had changed from a macrocytic type to a simple microcytic type The patient did not cooperate to the extent of eating a full diet The cutaneous lesions failed to heal entirely This case must be classified as a clinical failure

CASE 9—A B, a 45 year old housewife, was admitted to the neurologic division of St Mary's Hospital in St Louis in September 1942, at which time her chief complaint was dry and scaly skin of five weeks' duration, generalized weakness, especially in the legs, gradual loss of memory and an inability to think clearly of about two weeks' duration and emotional instability during the past several weeks A diagnosis of toxic cerebritis and avitaminosis was made by the attending psychiatrist

Because of an acute dermatitis which had developed during the period of hospitalization, dermatologic consultation was sought in October 1942 Examination revealed an acute erythematous dermatitis of the forehead, nasolabial folds, ears, neck, shoulders and arms All other areas of the skin were dry and rough The tongue was thick and dry but not denuded She gave a history of having a poor appetite and an inadequate diet Itching was a distressing symptom

While in the hospital, the patient had been given a high caloric high vitamin diet and thiamine hydrochloride (10 mg) by mouth, 300 mg of nicotinic acid was given intravenously, and nicotinic acid and riboflavin were administered by mouth With this therapy the mental symptoms improved, but there was no change in the dermatologic findings

Laboratory examination of the blood in October 1942 revealed the following values white blood cell count 8,275, red blood cell count 3,670,500, hemoglobin content (Sahli method) 12.5 Gm, mean corpuscular volume 113 cubic microns, mean corpuscular hemoglobin 34 micromicrograms and mean corpuscular hemoglobin concentration 30 per cent The color index was 1, saturation index 0.95 and volume index 1.2 The differential count was within normal limits The blood smear showed anisocytosis and poikilocytosis The Kahn reaction of the blood was negative

The patient was given vitamin A, 150,000 U S P units daily by mouth, and 3 cc of crude liver extract

containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly Later, vitamin B complex and liver extract were administered by mouth

After five weeks of intensive treatment, examination of the blood revealed the following values red blood cell count 4,542,000, hemoglobin content (Sahli method) 11.5 Gm, mean corpuscular volume 83 cubic microns, mean corpuscular hemoglobin 25 micromicrograms and mean corpuscular hemoglobin concentration 30 per cent The indexes were at normal levels The cutaneous lesions had greatly improved, and the itching had subsided

Treatment was continued for an additional four months At the end of this period the lesions of the skin had disappeared entirely and the patient had regained her normal mental and emotional balance

CASE 10—W H, a 57 year old housewife, consulted me in July 1943, complaining of an itchy dermatitis of the sides of the neck which had been present for several weeks A chronic, thickened, pruritic dermatitis of one year's duration was present on the dorsum of the left foot

She had suffered from diabetes mellitus since 1934 She had been obese for many years and gave a history of having reduced from 270 to 200 pounds (122.5 to 90.7 Kg) with the aid of thyroid (10 grains [0.65 Gm] daily) and diet Her weight at the time she was first seen was 230 pounds (104.3 Kg)

She was under the care of Dr Samuel B Grant, who reported the presence of vascular hypertension (200 systolic and 120 diastolic) Blood sugar levels varied from 231 to 143 mg per hundred cubic centimeters Sugar did not appear in the urine unless the blood sugar level was over 200 mg

In March 1943 the patient began a reducing diet, which produced a change in weight from 233½ to 217½ pounds (106 to 98.7 Kg) by August 1943 At this time the diet was supplemented by two multiple vitamin capsules daily It was during the period in which she was on a reducing diet supplemented with vitamin capsules that an acute dermatitis developed on the sides of the neck

Dermatologic examination of the lesions revealed a dry, scaly, pruritic dermatitis on the sides of the neck and a dry, thickened, scaly, pruritic dermatitis on the dorsum of the left foot

Laboratory examination of the blood revealed the following values white blood cell count 9,225, red blood cell count 4,775,000, hemoglobin content (Sahli method) 14.5 Gm, mean corpuscular volume 110 cubic microns, mean corpuscular hemoglobin 30 micromicrograms and mean corpuscular hemoglobin concentration 28 per cent The color index was 0.9, saturation index 0.83 and volume index 1.2 The differential count was within normal limits

The patient was given a well balanced diet and vitamin B complex by mouth, and 1.5 to 3 cc of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly At the end of two months' treatment, the lesions of the skin had disappeared and the hematologic values were within normal limits

CASE 11—R C, a woman aged 39, a bookkeeper, consulted me in March 1944, complaining of an itchy dermatitis of the sides of the neck which was of four days' duration The original attack had appeared about two months previously The patient stated that she had no desire to eat and that she was nervous and a poor sleeper She lived alone and prepared her own meals The diet was deficient in meat and eggs She had had

no gastric upsets. She said that she had had erythema multiforme when a child and two major operations within the past fifteen years. For the past two years, to avoid indigestion, she had taken sodium bicarbonate after each meal.

Examination of the cutaneous lesions revealed dry, scaly, pruritic, round and oval patches of dermatitis on the sides of the neck (fig 2), the suprascapular areas, the anterior surface of the chest and the arms adjacent to the axillary folds. The tongue appeared normal in color. The mucosa of the mouth was normal. The nails were brittle but normal in shape. There were Bitot spots present in both eyes.

Examination of the blood revealed the following values: white blood cell count 8,882, red blood cell count 4,237,500, hemoglobin content (Sahli method) 12 Gm, mean corpuscular volume 84 cubic microns, mean corpuscular hemoglobin 28 micromicrograms and mean corpuscular hemoglobin concentration 33 per cent. The indexes were normal, and the differential count was within normal limits.

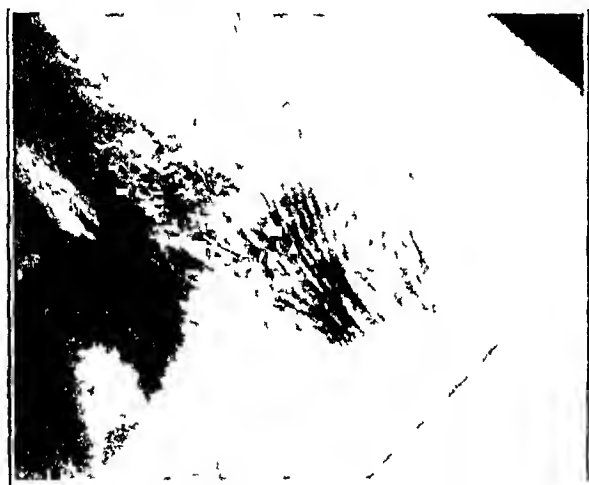


Fig 2—Lesions characteristic of the early stages

The patient was given 150,000 U. S. P. units of vitamin A daily by mouth and 25 cc. of crude liver extract containing 2 hemopoietic units per cubic centimeter was given intramuscularly twice weekly. She was placed on a well balanced diet. After two weeks' treatment, the itching stopped and the lesions healed.

#### DIFFERENTIAL DIAGNOSIS

The objective observations and the symptoms of severe pruritus made the differential diagnosis between nutritional dermatitis and contact dermatitis extremely difficult. The determination of the existence of macrocytic anemia in these patients was the only evidence, except a history of inadequate diet, to support or confirm the clinical impression. Once the presence of macrocytic anemia was established, treatment of a specific nature with crude liver extract produced rapid results.

Sensitization to actinic rays, on exposure to light, results in dermatitis of the exposed skin. This factor, while possibly present to some degree, as in other deficiency diseases, such as

pellagra, was not considered as a major etiologic agent. The onset of the disease in these patients, who were all indoor workers, was in the winter-time in 8 cases. There was no direct exposure to the sun. The disease occurred on the covered parts also. Five patients for whom the diagnosis of photosensitization not induced by topical sensitizing agents was made had normal hematologic values and did not respond to parenteral injection of liver extract.

The difference in objective signs, the absence of macrocytic anemia in 6 patients with cheilosis which responded to riboflavin and the failure of riboflavin to influence the dermatitis in case 1 were sufficient to exclude ariboflavinosis from consideration.

Schollitic dermatitis was eliminated from consideration because the dermatologic criteria necessary for such a diagnosis were not present.

A similarity in clinical findings seemed to link these cases with some of those which were observed by Gross<sup>2</sup> and reported as cases of non-pellagious eruptions due to deficiency of vitamin B complex. Of the larger group, 31 cases, in which a diagnosis of deficiency dermatitis was made, many fell into the five classifications which he enumerated.

In addition, 126 persons, including 15 with ane, 12 with contact dermatitis, 4 with eczema, 8 with dermatitis herpetiformis, 5 with lichen planus, 20 with neurodermatitis, 6 with lupus erythematosus, 10 with psoriasis and 1 to 4 each with nineteen other dermatologic diseases were examined. Twenty-four per cent were found to have an increase in the mean corpuscular volume and 7 per cent had microcytic hypochromic anemia.

#### SUMMARY AND CONCLUSIONS

Hematologic studies were performed on 179 patients presenting various dermatologic diseases with a view to determine the presence of macrocytic anemia, especially in persons in whom a deficiency of one or more fractions of the vitamin B complex was presumed to be a causative agent.

Forty-two patients presented lesions which did not conform to any dermatologic entity. Thirty-one of this group were ultimately classified as having eruptions which were due to vitamin B complex deficiency. Determination of the mean volume of the red cells proved to be an aid in the diagnosis in 22 (52 per cent) of these cases.

The response of the clinical symptoms, the improvement in the patients' general well-being and the drop in the mean corpuscular volume in all instances as a result of the parenteral injection of crude liver extract led to the conclusion that these patients present a syndrome of dis-

ease which is, at least in part, a result of a nutritional deficiency. The deficient substance is present in liver extract.

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#### ABSTRACT OF DISCUSSION

DR DUDLEY C SMITH, Charlottesville, Va. Vitamin B complex is, as its name implies, made up of many factors. It was already known that deficiencies in this nutritional complex cause many variable clinical and laboratory syndromes. There is presented in this paper another type of cutaneous abnormality associated with hematologic changes resulting from deficiency in some fraction or fractions of this mixture. It would be an interesting problem to determine the exact detailed fraction or fractions involved. This preliminary report by Dr Stryker and his associate does not attempt to solve this detail. Do the essayists have any opinion on this phase of the subject? It may be that the fraction which causes the cutaneous change is different from the fraction which causes the blood abnormality. It certainly would seem to be different from the hemopoietic factor that is used for pernicious anemia, because the response to crude liver extract is better than that to the purified extract.

The pruritic erythroderma described resembles clinically a contact or irritative dermatitis. How many errors in diagnosis have we made in the past. The majority of cases with this skin picture is probably due to external irritation. Does this deficiency state make the skin more susceptible to irritation or does the lack of this fraction produce per se the skin inflammation?

If the skin is made more susceptible to irritation by this deficiency, then we may have a basic explanation for cutaneous contact allergy.

Simple laboratory tests for avitaminoses are not numerous. The association of a macrocytic anemia with the dermatosis described increases the possibility of accuracy in diagnosis. However, macrocytic anemia is also associated with other types of nutritional deficiency. The macrocytic anemias are due mainly to decreased blood production. There are two etiologic factors, namely, the intrinsic from the patient's tissues and extrinsic involving the diet. The macrocytic characteristic is seen in pernicious anemia, sprue, pellagra, occasionally in pregnancy, diseases of removal of part of the gastrointestinal tract, hepatic disease and hypothyroidism. Vitamins have some effect not only on the production and maturation of blood cells but, according to results of a recent investigation, on the activity of the cells themselves (Cottingham, E, and Mills, C A. Influence of Environmental Temperature and Vitamin Deficiency on Phagocytic Functions, *J Immunol* 47: 493-502 [Dec.] 1943).

Conclusions from clinical trial based on subjective symptoms may be erroneous, but in these cases prompt objective improvement in the abnormalities of the skin makes the therapeutic tests more significant.

Mild and subclinical nutritional deficiencies occur in a high percentage of the American population. A deficiency may be caused by any abnormal condition which (1) increases the need of the nutritional factor, i.e., fever, (2) interferes with the absorption or utilization of it, (3) causes its elimination too rapidly, in addition to (4) subnormal intake. Dietary fads and even many diets prescribed by physicians may result in persons' receiving too little of the necessary nutritive essentials.

# AMERICAN LEISHMANIASIS

## REPORT OF AN AUTOCHTHONOUS CASE

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American leishmaniasis has received scant attention in the literature of the United States, most of the reports having originated from South America, particularly Brazil. While up to 1943 approximately 30 cases of cutaneous leishmaniasis (oriental sore) had been reported from the United States and Canada (1), none of which (with 1 possible exception<sup>1c</sup>) were autochthonous, only 3 cases of American, or mucocutaneous, leishmaniasis had been recorded as occurring in the United States 1 of which was presumably autochthonous.

McEwen<sup>2</sup> in 1914 published the first case and, although he called the disease oriental sore, he was undoubtedly dealing with American leishmaniasis. The patient acquired the lesion while traveling in South America. In contradistinction to cutaneous leishmaniasis, the lesion proved resistant to therapy. Furthermore, differentiation between oriental sore and American leishmaniasis had not as yet been made.

Wile,<sup>3</sup> during a discussion in 1942, mentioned that he had recently seen a patient with American leishmaniasis which was contracted in Brazil. No further details were given.

Recently Benedek<sup>4</sup> reported in an English journal a case from Chicago, which he considered to be the first autochthonous case of American leishmaniasis in the United States. However, there is some doubt as to the correctness of this idea. The patient had spent four years in Poland fifteen years prior to the development

of mucocutaneous lesions of the nose. Fox,<sup>5</sup> in discussing this case, declared that if the disease was really American leishmaniasis the patient had apparently contracted it in Poland.

The excellent contributions of Howard Fox<sup>6</sup> to American literature on mucocutaneous leishmaniasis were based on studies and observations made during trips to South America and should be consulted by any one interested in the disease.

American leishmaniasis is endemic in South America (except Chile), Central America and the state of Yucatan, Mexico. Many local names have accordingly been given to this disease. *Espundia* and *uta* are names frequently encountered in the textbooks, however, it is the consensus that these are merely local terms for mucocutaneous leishmaniasis.

The disease usually begins as an erythematous maculopapular or vesicular lesion on an exposed part of the body. This lesion frequently follows an insect bite or slight traumatism. Later a nodule forms, which, as a rule, undergoes ulceration. The ulcers may be few or, rarely, numerous. Generally there are several. The ulcers are round or oval, have a slightly raised firm border and may or may not be crusted. The granulating base is bathed with a moderate amount of secretion. Verrucous and papillomatous forms have been described. When healing occurs, a conspicuous pliable depigmented scar remains. The ulcers heal spontaneously, some within seven or eight months and others lasting for two or three years. This period has been designated as constituting the primary stage, and the lesions have been referred to as chancres.

In 10 to 20 per cent of the cases, after a period ranging from eight or nine months to fifteen years, the mucous membrane of the nose and/or throat is involved. This period is known as the tertiary stage. When, as occasionally happens, the chancres and oral lesions occur in rapid

1 (a) Dwork, K. G. Cutaneous Leishmaniasis (Oriental Sore) in the United States and Canada, Arch Dermat & Syph **45** 676 (April) 1942. (b) Silverberg, M. G., and Henschel, E. J. Oriental Sore in the United States, *ibid* **46** 705 (Nov.) 1942. (c) Gelber, A. Oriental Sore Possibly Contracted in the United States, *ibid* **46** 739 (Nov.) 1942.

2 McEwen, E. L. Oriental Sore in the Americas with Report of a Case, J Cutan Dis **32** 275, 1914.

3 Wile, U. J., in discussion on Ebert, M. H. A Case for Diagnosis, Arch Dermat & Syph **46** 606 (Oct.) 1942.

4 Benedek, T. American Leishmaniasis, J Trop Med **43** 147 (June 1), 164 (June 15) 1940.

5 Fox, H., in discussion on Benedek, T. American Leishmaniasis, Arch Dermat. & Syph **43** 1093 (June) 1941.

6 Fox, H. (a) American Leishmaniasis, Arch Dermat & Syph **23** 480 (March) 1931, (b) American Leishmaniasis, *ibid* **30** 241 (Aug.) 1934.

sequence, the latter are regarded as secondary lesions<sup>7</sup>

The nose, particularly the nasal septum, is most frequently involved, the pharynx and larynx are less often affected. Rarely, the mucous membranes of the esophagus, cheeks and tongue are attacked. According to Fox,<sup>6</sup> the disease begins with congestion, followed by infiltration, vegetation and superficial ulceration. Destruction of the cartilage of the nasal septum results in flattening and distortion of the nose. Occasionally a verrucous type is encountered, the lesion of which may resemble rhinophyma, lupus vulgaris or blastomycosis.

When untreated, the lesions of the mucous membrane show almost no tendency to heal. After years of suffering the patient may die from exhaustion and cachexia.

It is generally agreed that the organism causing American leishmaniasis is *Leishmania braziliensis*, although morphologically it is identical with *Leishmania tropica*, which is responsible for oriental sore. Some observers, however, hold to the opinion that the organisms are not different and distinct species. Benedek,<sup>4</sup> for example, constantly referred to *L. tropica* as the causative organism of American leishmaniasis. Agglutination tests carried out by Noguchi<sup>8</sup> apparently showed that the causative organism of American leishmaniasis differed from the organism producing oriental sore. Later investigators have doubted that the experiments were adequately controlled. At present the controversy remains.

The vector responsible for the transmission of the disease is thought to be the sand fly (*Phlebotomus*). There are over fifty known species of *Phlebotomus*, of which more than twenty are found in the Americas. Of these, only three have been reported from the United States. *Phlebotomus vexator* has been collected from along the Potomac River and from Ansley, La., *Phlebotomus diabolicus*, from Del Rio, Sonora and Uvalde, Texas, and *Phlebotomus texanus* from San Antonio, Texas.<sup>9</sup> It is interesting to note that all of these reports save one have come from or near the state of Texas.

The micro-organism, *L. braziliensis*, is found but sparsely in smears and sections, differing thus from *L. tropica*, which is seen in great numbers in oriental sores. In sections of the skin or mucous membrane the organism is usually found within large mononuclear cells or free in the tissue spaces, although it is occasionally seen within polymorphonuclear leukocytes and endothelial cells. It has also been observed in affected lymph nodes. Benedek<sup>4</sup> claimed to have demonstrated the organism for the first time in the peripheral circulation by means of the cantharis blister method. Moreover, he reproduced mucocutaneous leishmaniasis in guinea pigs by inoculating the contents of the cantharis blister. This would indicate, as some authors have steadfastly maintained, that American leishmaniasis is a systemic infection and that the late mucocutaneous lesions are due to metastasis rather than to direct transfer of the organism. We favor the latter viewpoint.

When present, the organism is rather easily identified in smears and sections as a round or oval body 2 to 4 microns in diameter, containing a round trophonucleus and a smaller round or rodlike kinetonucleus. It is readily grown on N N N medium. When cultured, it assumes a flagellate form. Reproduction is by longitudinal division, although Benedek<sup>4</sup> and Lanteri<sup>10</sup> observed multiplication also by budding.

The histologic picture is not distinctive. Studies show merely a chronic inflammatory reaction with granulation tissue. At times it may resemble the tuberculoid structure of syphilis or tuberculosis.

Antimony and potassium tartrate injected intravenously and stibophen intramuscularly are the common therapeutic agents. Fox mentioned that a French arsenical preparation resembling arsphenamine had given better results in Brazil. Roentgen rays are apparently of some value. Whereas the cutaneous lesions generally respond satisfactorily to treatment, the mucocutaneous lesions frequently resist all therapy.

#### REPORT OF CASE

M. M., an American-born Mexican boy aged 6 years, was first seen on Oct. 10, 1942. At that time he complained of ulcers on the dorsum of both feet, on the right knee and on the buttocks of approximately seven months' duration. The first lesion appeared on the dorsum of the left foot and was described as an erythematous papule which the parents considered to be an insect bite. This gradually enlarged and ulcerated.

10 Lanteri, G. Peculiar Reproductive Types of *Leishmania Tropica* in Case of *Furunculus Orientalis*, *Gior ital di dermat e sif* 69:925, 1928, cited by Benedek<sup>4</sup>

7 Weidman, F. *Leishmaniasis Americana*, in Blumer, G. *The Practitioners Library of Medicine and Surgery*, New York, D. Appleton-Century Company, Inc., 1936, vol. 10, p. 289.

8 Noguchi, H. Action of Certain Biological, Chemical and Physical Agents upon Cultures of *Leishmania*. Some Observations on Plant and Insect Herpetomonads, in *International Conference on Health Problems in Tropical America*, Boston, United Fruit Company, 1924, cited by Fox.<sup>5</sup>

9 Carpenter, J. M. Personal communication to the authors.



Four months later a similar papule appeared on the dorsum of the right foot, followed shortly by a lesion on the extensor surface of the right knee and one on the right buttock. These, in turn, became ulcerated and crusted. The patient had few subjective symptoms.

The boy had been born on a ranch near Alice, Texas, and had never traveled more than 60 miles (96.5 kilometers) from his birthplace. Otherwise, the past history was of no importance.

*Family History*—The father and mother, both of whom were living and well, had been born in the United States. The patient had three brothers and three sisters, who, likewise, were well and free from cutaneous disease. None of the family had ever visited Mexico.

*Physical Examination*—Examination in October 1942 revealed a round ulcer on the dorsum of the left foot,

of which 34 per cent were mature and 3 per cent stab cells, lymphocytes, 56 per cent, monocytes, 2 per cent, eosinophilic leukocytes, 4 per cent, and basophilic leukocytes, 1 per cent. The urine was normal on examination.

Smears of the exudate taken from several ulcers and stained with Gram's stain showed no leishmaniasis. Cultures of the exudate made on both Sabouraud's and N N N mediums were negative.

Roentgenologic examination of the chest showed no abnormality.

*Microscopic Examination*—The first histologic examination of tissue removed from the large ulcer revealed only a nonspecific chronic granuloma. Later, the second specimen for biopsy was taken from the smaller ulcer on the dorsum of the right foot and stained with hematoxylin and eosin (fig 1). As before, the microscopic picture was that of chronic granulation

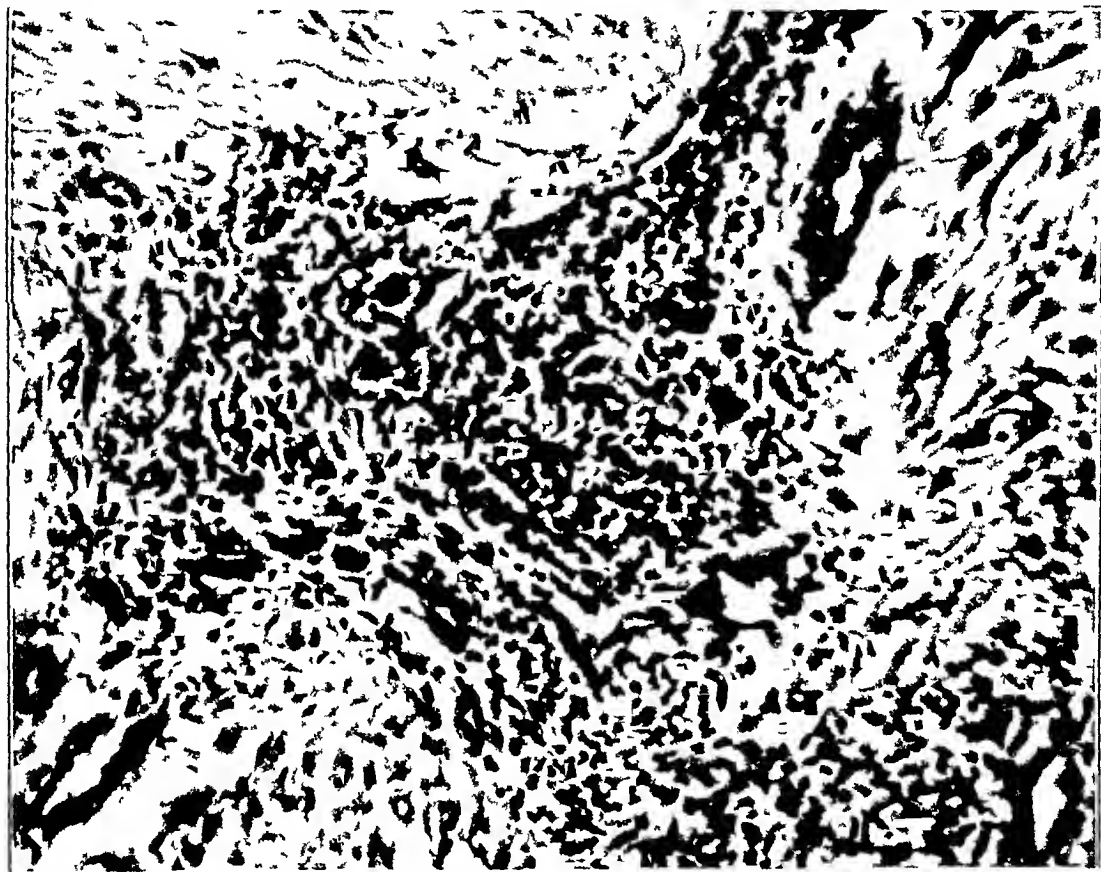


Fig 1—Low power photomicrograph of a section from the ulcer on the right foot. Hematoxylin and eosin stain.

approximately 3 cm in diameter, which was covered with a thick dark crust. Removal of the crust showed a granulating base bathed with a moderate amount of secretion. The border was raised, firm and sloping. There was only slight tenderness to pressure. On the dorsum of the right foot there was a similar but somewhat smaller ulceration. The extensor surface of the right knee and the right buttock each presented a slightly raised dry crusted lesion of about 1 cm in diameter. Routine physical examination gave essentially negative results except for a generalized lymphadenopathy.

*Laboratory Examination*—The Wassermann and Kahn reactions of the blood serum were negative. Examination of the blood showed hemoglobin content, 86 per cent, color index, 1.04, erythrocytes, 4,180,000, leukocytes, 8,350, polymorphonuclear leukocytes, 37 per cent,

tissue, the cellular infiltrate consisting mainly of macrophages, plasma cells and lymphocytes, with a few eosinophils. In addition, however, there were many small, round, clear bodies containing a prominent dark-staining round macronucleus and a smaller rod-shaped micronucleus, which was not so easily demonstrated (fig 2). These bodies were found within large mononuclear cells, vascular endothelial cells and the lumens of small lymphatic vessels and lying free in the tissue spaces.

*Course*—From January 1943, when the diagnosis of American leishmaniasis was made, until July 1943 the patient was lost from observation. Examination on July 4, 1943 revealed the cutaneous ulcerations to be entirely healed with the exception of the large lesion on the dorsum of the left foot. This lesion had almost

disappeared and was considered not worthy of photographing. The sites of the healed ulcers were represented by conspicuous, slightly erythematous, atrophic-looking scars.

The results of a general physical examination, including examination of the mucous membrane of the nose and throat, were again normal except for the persistence of a rather pronounced generalized lymphadenopathy.

The boy's parents attributed his "cure" to the local use of herbs.

The patient was not seen again until May 28, 1944. The skin at this time was clear except for depigmented atrophic scars at the sites of the former lesions. The generalized lymphadenopathy remained but was not so

Unfortunately, we were unable to demonstrate the organism in smears or cultures, either from the cutaneous lesions or from the peripheral circulation, as Benedek claimed to have done. Perhaps we should have succeeded had the patient been available for more intensive and repeated studies.

We have little doubt that the ulceration of the nasal septum represents the beginning of the tertiary stage of the disease. The appearance and location of the lesion is typical for American leishmaniasis.



Fig 2—High power photomicrograph of a section from the ulcer on the right foot, showing *L. braziliensis*. Hematoxylin and eosin stain.

conspicuous as before. Careful examination of the mucous membranes revealed a superficial ulceration, several millimeters in diameter, on both sides of the anterior portion of the nasal septum. There were no subjective symptoms.

Smears and cultures of the serum obtained from an anthrax blister were negative for leishmaniasis.

#### COMMENT

Although regional lymphadenopathy in American leishmaniasis has frequently been mentioned in the literature, we found no reports of generalized lymphadenopathy such as was present in our case. The enlargement was striking even from a distance. This was still present almost a year later, although not to the same degree.

It is our opinion that the apparent rarity of the disease in the United States, with only 1 previously identified case, is probably not genuine. If the disease is kept in mind and a diligent persistent search made for the organisms, it is conceivable that many more cases will be discovered, especially in Texas and the Southwestern states bordering on Mexico. Furthermore, it is quite probable that the distribution of the supposed vector, a phlebotomus, is more general than has been reported, as there has apparently been no concerted effort to collect sand flies.<sup>9</sup> To date only three species have been identified from the United States. McEwen as early as

1914 expressed the belief that oriental sore (meaning American leishmaniasis) would probably become endemic in certain sections of the southern states. Today, with numerous military and civilian personnel returning from the endemic areas, we are more than ever inclined to expect the fulfillment of his prediction.

#### SUMMARY

An autochthonous case of American leishmaniasis with involvement of the lower extremities and nasal septum was encountered in the state of

Texas. Three species of the supposed vector, *Phlebotomus*, have been identified in the United States, all of which are found within or near Texas. It should be remembered that the apparent rarity of the disease in the United States is probably not real. The return of military and civilian personnel from endemic centers is further reason for keeping American leishmaniasis in mind.

Dr S W Becker and Dr Howard Fox examined the histologic sections, and Dr S W Becker made helpful suggestions regarding the manuscript.

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# KAPOSI'S VARICELLIFORM ERUPTION

## EXTENSIVE HERPES SIMPLEX AS A COMPLICATION OF ECZEMA

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By a series of observations some months ago I was led to the conclusion that the virus of herpes simplex when implanted on diseased skin may result in an eruption of greater severity and extent than the usual group of herpetic vesicles. My attention was first directed to this subject by observation of the eruption the course of which is here described.

CASE 1—M L, 2½ years of age, had had atopic eczema for many months, present in a mild form in each cubital area as a papular eruption with occasional exudative manifestations. The course of the eruption changed suddenly, with no evident relation to environmental or dietary changes, when one arm suddenly presented increasing redness, swelling and a papular outbreak. The lesions soon became discrete tense vesicles of a size and tenseness greater than are usually observed in eczematous eruptions. Associated with the development of fever and general toxemia, the eruption extended over the eczematous area and about 1 cm beyond on the previously normal skin. The area involved was approximately 5 cm in diameter. After four or five days the vesicles dried in situ and redness and swelling gradually disappeared, leaving the eczema about as before the incident.

In this case the diagnosis of herpes simplex was suggested by a history of exposure to the virus. For about three days before the onset of the child's illness the father had suffered from herpes simplex of an eyelid accompanied by herpetic conjunctivitis. (Smears from the conjunctivas contained no eosinophilic leukocytes or pyogenic bacteria.) At the same time the mother suffered from several aphthous ulcers of the mouth. With this evidence of probable exposure to the herpetic virus a diagnosis of herpes simplex was made, though this diagnosis seems not to be commonly considered in cases of febrile erythematous and vesicular exacerbations of eczematous eruptions.

Within a short time 3 other persons were observed during periods of more severe febrile exacerbations of their eczematous eruptions.

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There was striking resemblance of these cases to the preceding case, and a similar diagnosis was made in each instance.

CASE 2—Mrs T H, aged 20 years, had had perennial eczema on the arms and hands for seven years and seasonal rhinitis due to sensitivity to ragweed pollen. The eruption extended to the face and neck during the pollen season of 1943 but was greatly improved by October 1. On October 20 she complained of suddenly increased redness and swelling of the face, and when seen on October 22 she presented an extensive eruption of tense vesicles accompanied with submental adenopathy. The eruption became more severe requiring her admission to the hospital on October 24, when the temperature was 102.4 F, it was 101 F on the following day. The eruption improved promptly, the temperature becoming normal by October 27, and the patient left the hospital October 29. On her admission to the hospital the white blood cell count was 7,000 per cubic millimeter.

Labial herpes simplex preceded by two days the sudden change in this patient's eruption.

CASE 3—I first saw R J, a 10 months old child, on Oct 26, 1943, when there were scaling and redness of the face with some areas of exudation. The hands were red, swollen, crusted and fissured. Scaling papular plaques were present on the thighs and knees. The eczematous eruption had been present for eight months. The mother was advised to apply compresses moistened with a dilute solution of copper and zinc sulfates and was given a phenolized paste of zinc oxide for the areas where exudation was absent. On October 28 the eruption became much worse and the rectal temperature was 104 F. On October 29 the temperature was 104.5 F and there were increased redness and swelling associated with numerous tense vesicles on the right cheek, the eyelids and the right hand. Axillary adenopathy was present. Use of the wet dressings was continued. The temperature was 102 F on October 31 and 101 F on November 1, when the eruption was greatly improved but had extended at its periphery. Most of the vesicles had ruptured, leaving bright red moist bases. By November 5, ten days after the onset, the eroded areas were healing steadily, though redness and slight swelling were still present.

The mother of this child had had labial herpes simplex for two days before the child's eruption appeared. During the early course of the eruption another physician prescribed oral use of sulfathiazole, which failed to exert a noticeable influence.

CASE 4—Mrs C P K, aged 54 years, had had generalized neurodermatitis for several months, and the eruption had been improving slowly and steadily in the hospital for four weeks. Numerous bright red discrete papules appeared suddenly on the face on April 18 and changed to small tense vesicles, a few of which were umbilicated by April 20 (fig 1). Biopsy was performed on April 21 and fluid removed for animal inoculation. On April 22 each vesicle was crusted and the redness and swelling had disappeared. The temperature was 99.6 F on April 20 and 100.4 F on April 21. The white blood cell count was 8,900 on April 21. This patient knew of no exposure to vaccinia or herpes simplex. A microscopic section of cutaneous tissue showed a unilocular vesicle resulting from epithelial degeneration and separation of the epidermis from the cutis (fig 2). There was evidence of ballooning degeneration and nuclear degeneration. The cellular infiltration extended deeply in the cutis,



Fig 1 (case 4)—An extensive vesicular eruption was superimposed on a chronic eczematous background. Umbilicated vesicles are visible on and near the ear and near the eye, other tense vesicles may also be seen, but the majority of the vesicles had ruptured.

which was edematous and slightly infiltrated by lymphocytes, probably owing more to the underlying eczema than to the acute complication. The pathologic process corresponded to previous descriptions of severe herpes simplex.<sup>1</sup>

The presence of herpetic virus was demonstrated by experimental studies which will be discussed later.<sup>2</sup> In none of these 4 cases was

there a history of recent exposure to vaccinia. The 2 children had not been vaccinated. Each of the 2 adults had been successfully vaccinated only once in childhood. These cases were discussed in a brief report before the Ramsey County Medical Society, on April 24, 1944.

In each case the acute herpetic vesicular eruption could have been confused with an acute exacerbation of the eczema or a secondary pyogenic infection. Eczematous exacerbation was ruled out by the absence of a precipitating factor, involvement of only part of the pre-existing eruption, presence of fever and toxemia and prompt recovery to the earlier state of the eczema. Pyogenic infection was unlikely in the first case because the eruption improved promptly and steadily without treatment by antiseptics. In the third case there was a failure to respond to oral administration of sulfathiazole.

After a discussion of these cases with other dermatologists it became evident that "herpetization" of eczema has not been commonly recognized. A number of textbooks were then reviewed in an unsuccessful attempt to find references to such eruptions in discussions of eczema or herpes simplex, a fact which suggested that their counterparts must have been regarded previously in some other light. An unrelated condition was discussed in the volumes edited by Darier with brief reference to "vacciniform herpes (Fournier)," an eruption resembling perianal pyoderma.<sup>3</sup> The term "herpetoid eczema" has been used by Sutton and Sutton but only with reference to nummular eczema.

The only personal clinical experiences with conditions comparable with those of the 4 cases herein described were with eczema vaccinatum. This subject was thoroughly reviewed by Tedder,<sup>4</sup> who reported several such cases and described the usual clinical course. After vaccination in the presence of eczema or some other itching eruption there follow redness and swelling and then occurs an outbreak of vesicles which become purulent and umbilicated. Crops of vesicles continue to appear for several days or a week and then become crusted, finally healing with pigmentation and development of pitted scars. This eruption is accompanied with painful swollen lymph nodes, general malaise and high fever, death occurring when the disease is severe.

There seems to be justification for Tedder's conclusion that eczema vaccinatum in most instances represents exogenous inoculation with

1 Schonfeld, W. Herpes Simplex, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1928, vol 7, pt 1, p 83.

2 Dr Charles A. Evans, of the department of bacteriology, made the experimental studies which resulted in identification of the herpetic virus in this case.

3 Darier, J, and others. *Nouvelle pratique dermatologique*, Paris, Masson & Cie, 1936, vol 8, p 288.

4 Tedder, J. W. Eczema Vaccinatum, *Arch Dermat & Syph* 34 1008 (Dec) 1936.

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the vaccinal virus on eczematous skin, but it is less certain that Kaposi's varicelliform eruption and pustulosis vacciniformis acuta are synonyms of eczema vaccinatum. Certainly in some cases the latter terms have been used to describe eczema vaccinatum when there was no history of vaccination, but the clinical features of the three diseases are not always identical. If eczema vaccinatum and Kaposi's varicelliform eruption are synonymous, it is difficult to understand why

eralization and erythema multiforme. In a number of instances pyogenic organisms appear to have caused similar eruptions, resulting in an epidemic in the series reported by McLachlan and Gillespie.<sup>5</sup> Having observed the superimposition of herpes simplex on eczematous eruptions, I believe that the same sequence occurred in certain cases previously reported under the titles proposed by Kaposi,<sup>6</sup> Juliusberg<sup>7</sup> and others.



Fig 2—Photomicrograph of a section of tissue from a vesicle (case 4). A, a unilocular vesicle with epithelial degeneration and underlying cellular infiltration, B, degenerative changes in the epithelial cells characteristic of viral diseases.

experienced dermatologists have disagreed so frequently as to the nature of the latter disease. In some cases it has been assumed that the vaccinal virus was borne to the skin through the blood, in others it was thought to have been spread by unrecognized external contact. There is dissimilarity with reference to the history of previous, concurrent or subsequent vaccination. In many reports the lesions are said to have resembled several diseases rather than one that is, variola, varicella, vaccinia, zoster with gen-

Kaposi's original contribution provided a clear and concise description which may profitably be repeated here. He observed at least 10 children

<sup>5</sup> McLachlan, A. D., and Gillespie, M. Kaposi's Varicelliform Eruption. Epidemic of Sixteen Cases, Brit J Dermat 48 337, 1936.

<sup>6</sup> Kaposi, M. Pathology and Treatment of Diseases of the Skin, ed 4, translated by J. C. Johnston, New York, William Wood and Company, 1895, p 346.

<sup>7</sup> Juliusberg, F. Ueber Pustulosis acuta varioliformis, Arch f Dermat u Syph 46 21, 1898.



with an acute outbreak of numerous vesicles, partly scattered and partly arranged in groups

The vesicles are as large as a lentil, filled with clear serum, and the majority are umbilicated. They look like varicella vesicles but undoubtedly do not belong to this class. The integument which has been attacked in this manner now appears still more swollen, even tense. The little patients have high fever (40° C or more) and are very restless. The vesicles develop very acutely (sometimes over night), in large numbers, and often continue to appear, in successive crops, for three or four days or even a week. Those which appeared first undergo desiccation, rupture, and expose the corium, or they become encrusted and fall off. The largest number of these varicella-like vesicles are found on already eczematous skin, but smaller groups appear upon the previously intact skin of the neighborhood, upon the forehead, ear, neck, and even the shoulders and arms.

Death followed involvement of the nervous system in at least 1 of the 10 cases. The presence of swollen, tender regional lymph nodes was not mentioned by Kaposi but has been described by numerous subsequent writers.

Barton and Brunsting<sup>8</sup> recently provided a thorough review of the literature on Kaposi's varicelliform eruption. They reported that atopic dermatitis was present in 80 per cent of the cases and in 75 per cent the patients were under 4 years of age. The mortality rate was 25 per cent, being much higher in children than in adults.

Certain of the older reports were reviewed in a search for mention of herpetic associations. In none is there a clear history of presence of herpes simplex in the patient or his associates, but some of the descriptions have resemblance to the cases I have reported here. It is possible that Juliusberg's case is an example of herpetic inoculation on an eczematous background.<sup>7</sup> The mother of the patient had on one eyelid an eruption the nature and course of which suggest the possibility of herpes simplex. (The eruption was not seen by Juliusberg, and the description was provided by another physician, all dermatologists know how frequently physicians fail to recognize herpes of the eyelids.) She had previously been vaccinated on two occasions, hence it is unlikely that an accidental inoculation with vaccinal virus would have resulted in primary vaccinia. If the mother's eruption was herpetic, that of the child may have been also. In describing a herpetic eruption on an eyelid Andervont and Frieden-

wald<sup>9</sup> pointed out that had the herpetic virus not been demonstrated the eruption "would have been regarded as a typical example of accidental infection with vaccine virus." The photograph of their patient shows an eruption the description of which would match that of the mother of Juliusberg's patient.

In the case of the child described by Freund<sup>10</sup> there had been no previous vaccination and after the disappearance of the vesicular eruption it was possible to inoculate successfully with vaccinia. Freund mentioned the possibility of eczema vaccinatum's being confused with herpes simplex but excluded the latter diagnosis because the herpetic virus was not demonstrated and delling was present, though he pointed out that delling is sometimes observed in herpes simplex. In a number of other reports subsequent vaccination was successful.

Goeckerman and Wilhelm<sup>11</sup> described an eruption much like that of Mrs. T. H. (case 2), but there was no note of apparent relationship to herpes simplex. As in my case, the vesicular eruption was preceded by redness and swelling for two days, the course was brief, only a few of the lesions were delled and pustulation was not present.

Under the title "Kaposi's Varicelliform Eruption" Corson and Ludy<sup>12</sup> reported 3 cases, in the first the possibility of herpes may be suspected because of the presence of coryza, limitation of the eruption to one cheek and absence of scarring.

Since Kaposi<sup>6</sup> originally suggested "eczema herpetiforme" as the name for the disease which has since been spoken of as a "varicelliform eruption," it is ironic that its cause should have remained obscure for forty-five years while it was confused with vaccinia and other infectious diseases. However, in 1941 Seidenberg<sup>13</sup> described experimental studies in 2 cases which he reported under the title of "Pustulosis Vacciniformis Acuta." In the study of the first case he successfully inoculated the cornea of a rabbit, producing an inflammatory reaction from which subsequent

9 Andervont, H. B., and Friedenwald, J. S. A Case of Vacciniform Blepharitis Due to an Atypical Herpes Virus, *Bull. Johns Hopkins Hosp.* **42** 1, 1928.

10 Freund, H. Zur Aetiologie der Pustulosis vacciniformis acuta (Kaposi-Juliusberg), *Dermat. Wchnschr.* **98** 52, 1934.

11 Goeckerman, W. H., and Wilhelm, L. F. Kaposi's Varicelliform Eruption, *Arch. Dermat. & Syph.* **32** 59 (July) 1935.

12 Corson, E. F., and Ludy, J. B. Kaposi's Varicelliform Eruption. Report of Three Cases, *Am. J. Dis. Child.* **50** 1476 (Dec) 1935.

13 Seidenberg, S. Zur Aetiologie der Pustulosis vacciniformis acuta, *Schweiz. Ztschr. f. Path. u. Bakt.* **4** 398, 1941.

8 Barton, R. L., and Brunsting, L. A. Kaposi's Varicelliform Eruption, *Proc. Staff Meet., Mayo Clin.* **18** 199, 1943.

This publication is an abbreviated report. The more complete paper is to be published in the *ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY*. The authors kindly allowed examination of the unpublished manuscript and use of lantern slides illustrating their cases.

transfers were successful. In the study of the second case a series of rabbits were inoculated and subsequently shown to be immune to inoculation with the virus of vaccinia. Seidenberg concluded that the disease is not etiologically connected with vaccinia and is probably a manifestation of herpetic infection in a person with exudative diathesis.

Ronchese<sup>14</sup> recently reported a case as eczema vaccinatum. He mentioned Seidenberg's experimental studies but questioned whether Kaposi's varicelliform eruption would be so severe and so infrequent and would fail to recur if it were caused by the virus of herpes simplex. He concluded that "a relation of dermatitis vaccinica to herpes simplex is most unlikely."

On the basis of recent observation of 2 cases Barton and Brunsting<sup>8</sup> came to the same conclusion as I—that there is little support for a theory that such eruptions are caused by the virus of vaccinia but that there is more evidence to support the opinion that Kaposi's varicelliform eruption usually results from an eczematous person's reactions to the virus of herpes simplex. Both patients were adults having atopic dermatitis, each eruption was preceded by ordinary herpes simplex of the lip or chin. In 1 case there were signs and symptoms of involvement of the central nervous system, the patient was extremely ill and ultimately presented a generalized eruption. Virus from 1 patient was transferred to a rabbit, in which it produced herpetic keratitis, and then to a mouse, in which encephalitis developed. Serum of this mouse afforded effective protection to other mice later inoculated with lethal doses of herpetic virus.

In recent weeks there have been two additional reports. Wenner<sup>15</sup> described extensive eruptions in 3 infants with Kaposi's varicelliform eruption. From the lesions he obtained viruses which were identified as herpetic. Blattner, Heys and Harrison<sup>16</sup> have prepared a preliminary report of studies with a virus obtained from a patient recently observed by Dr. Clinton Lane.<sup>17</sup> This virus was inoculated on chorio-allantoic membranes of chick embryos, where it produced numerous small opaque pocklike lesions, from which the virus was transferred to mice and rabbits, in which it produced encephalitis.

14 Ronchese, F. *Dermatitis Vaccinica*, Arch Dermat & Syph **47** 613 (May) 1943.

15 Wenner, H. A. *Complications of Infantile Eczema Caused by the Virus of Herpes Simplex*, Am J Dis Child **67** 247 (April) 1944.

16 Blattner, R. J., Heys, F. M., and Harrison, M. *A Filterable Virus Isolated from a Case of Kaposi's Varicelliform Eruption*, Science **99** 432, 1944.

17 Lane, C. W. Personal communication to the author.

Vesicular contents from my fourth patient (M1s C P K) were inoculated on the scarified corneas of 2 rabbits. (The corneas of the opposite eyes were scarified but not inoculated, no keratitis developed there.) Typical herpetic keratitis appeared within forty-eight hours. After five days 1 rabbit was killed and the eye sectioned and stained, allowing demonstration of the eosinophilic intranuclear inclusion bodies of herpes simplex. The second rabbit acquired encephalitis with subsequent paralysis of the opposite lower extremity. After three weeks the second rabbit was killed and the blood used in neutralization experiments which determined the presence of antibodies against herpetic virus.

Each of 6 mice was inoculated with 0.05 cc of vesicular fluid, death resulting in seven to fifteen days. From their brains was obtained virus for inoculation into other mice. Immunologic and neutralization studies are still being carried out.

#### COMMENT

There remains little doubt that Kaposi's varicelliform eruption can result from inoculation with the virus of herpes simplex. The experimental studies reported by several previous authors and the contents of the present report are sufficient evidence that the herpetic virus can produce such an eruption as a complication of eczema and certain other diseases. This eruption varies in extent, but in the more severe forms it cannot be distinguished from the disorders described by Kaposi, Juliusberg and other observers under a variety of titles. It remains a question whether all previous cases should be regarded as examples of herpetic infection. I have listed a few instances in which the evidence favors that interpretation of the case. In other instances these eruptions may have represented eczema vaccinatum, though proof of the true cause was not demonstrable by a history of exposure to the virus of vaccinia. In still other cases the tense vesicles may have resulted from infection with pyogenic organisms. Perhaps further studies will demonstrate additional causes of such varicelliform eruptions.

It may be difficult to differentiate the several varicelliform eruptions. Tense vesicles and umbilication of the vesicles make it less likely that one is dealing with pyogenic infections.<sup>5</sup> Smears and cultures are inconclusive because pyogenic organisms may complicate viral infections. Biopsy can be used to differentiate pyogenic from viral eruptions, but herpetic and vaccinal eruptions cannot be distinguished with certainty. In a given case failure of an eruption to respond to therapy with sulfonamide compounds must be regarded as evidence suggestive of a viral cause.

Failures have been observed with sulfanilamide by Goeckerman and Wilhelm and with sulfathiazole by Barton and Brunsting (2 cases) and by me in case 3 of the present report. Stephen Epstein<sup>18</sup> administered both sulfadiazine and sulfathiazole to 2 infants and thought that the results suggested only that the drugs aided in control of the secondary infection. Connor and Gonce<sup>19</sup> reported inconclusive results.

Vaccinal and herpetic eruptions can probably be distinguished clinically in the majority of instances (experimental studies can be conclusive). The vesicles of eczema vaccinatum are as a rule fewer, larger and tenser, and more of them are pustular or umbilicated. The eruption and the general illness are longer than in cases of eczema herpeticum. The vesicles of eczema herpeticum are moderately tense, they tend to be grouped or to coalesce, and the majority do not develop umbilication. It is possible that involvement of the central nervous system is more frequently observed with herpetic infection, but both viruses are neurotropic to some extent. The lesions tend to rupture, if discrete, they may crust and heal, if more numerous, they coalesce as bright red erosions which heal by epithelization. In both diseases the progress of the viral disease is modified to some extent by the site, extent and severity of the previous eczema or other dermatosis.

Since so few cases have yet been proved to be examples of herpetic complication of eczema, it is impossible to estimate the prognosis or to describe the course in greater detail. Milder eruptions have been observed (case 1) and will perhaps be found to be more numerous than the severe eruptions.

#### SUMMARY

Infectious complications of eczema may be pyogenic or viral. "Kaposi's varicelliform eruption," "Juliusberg's pustulosis vacciniiformis acuta," "eczema vaccinatum," "impetiginized eczema" and other terms have been applied to these complications. By some writers the first three terms have been regarded as synonymous, but this opinion seems to be an error. Eczema vaccinatum is a distinct entity caused by the virus of vaccinia. Kaposi's and Juliusberg's terms probably apply to a group of disorders the clinical appearance of which is similar.

Of these patients at least some and probably many have eruptions resulting from implantation of the virus of herpes simplex on previously

disturbed skin. The background is usually that of eczema, but in some instances other dermatoses precede the acute eruption. The degree of severity may depend on the virulence of the virus, the susceptibility of the host and the nature and extent of the preceding eruption. In most instances it should be possible to recognize this condition by clinical observation. In describing 4 examples of herpetic complication of eczema I pointed out that the disease need not be severe (case 1).

The results of experimental studies confirm the data published by certain other workers.

In this report are described 2 cases in which the eruption was diffuse at the onset and the source of the infection was a parent with herpes simplex (cases 1 and 3). In case 4 the source of the infection was not determined, but the nature of the eruption was established by clinical observation, microscopical study of a vesicle and experimental studies with the virus obtained from vesicular contents. Most previously reported cases resemble case 4 in that the source of infection was not recognized because the eruption was diffuse and extensive when first seen. As in my case 2, Barton and Brunsting recognized labial herpes simplex in their 2 patients.

"Kaposi's varicelliform eruption" does not seem to be a suitable name for an eruption caused by the herpetic virus. There is no need for the name to point out the slight resemblance to varicella, no one believes the virus of varicella to be concerned in the development of these eruptions. Kaposi originally suggested that the eruption be spoken of as "eczema herpetiforme," but the eruption not only resembles herpes simplex—it is that disease in an extensive form. In cases in which the herpetic virus is incriminated and following the usage established by application of the term "eczema vaccinatum," Kaposi's varicelliform eruption could well be regarded as "eczema herpeticum" or spoken of as extensive herpes simplex complicating eczema (or other dermatoses).

#### ADDENDUM EXPERIMENTAL DATA WITH SUGGESTED THERAPEUTIC APPLICATION<sup>20</sup>

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The conclusion that the virus of herpes simplex caused the eruption in this case (case 4) is based on the following experimental evidence:

20 Aided by grants from the John and Mary R. Markle Foundation and the Graduate School of the University of Minnesota.

21 From the Department of Bacteriology of the University of Minnesota.

22 From the Division of Dermatology of the University of Minnesota.

<sup>18</sup> Epstein, S. Personal communication to the author.

<sup>19</sup> Connor, A., and Gonce, J. E., Jr. The Treatment of Kaposi's Varicelliform Eruption with Sulphonamide Drugs, *J. Pediat.* **24** 335, 1943.

Vesicle fluid collected on the third day of illness was inoculated into 5 mice intracranially. Four died on the sixth to eighth days with the appearance of having an encephalitis. Subsequent brain to brain passage resulted in a regularly fatal illness with the usual appearance of herpetic encephalitis in mice. Aerobic and anaerobic cultures proved the brains of infected mice to be bacteriologically sterile. The brain of 1 mouse was subjected to microscopic study. Typical herpetic intranuclear inclusion bodies were found in the nerve cells.

Corneal inoculation of 2 rabbits was performed with the same specimen of vesicle fluid as was used for inoculation of mice. At three days a severe purulent keratoconjunctivitis was present in the inoculated eye of each rabbit. One animal was killed at this time. Sections of the inoculated eye showed that most of the corneal epithelium had sloughed off. Near the limbus, remaining epithelial cells showed granular acidophilic intranuclear inclusions of the sort known to be caused by the virus of herpes simplex. At seven days in the second rabbit a disturbance of equilibrium developed that caused it to move in circles, going toward the side of the inoculated eye. On the eleventh day a paresis of the right hindleg was noted. At twenty days the disturbance of equilibrium and the paresis were still present.

A third rabbit (K 194) was inoculated by corneal scarification with brain from a mouse representing the second passage of the virus in mice. Again the typical keratoconjunctivitis and a moderate disturbance of equilibrium resulted. Serum collected two days and twenty-seven days after inoculation was tested for antibodies to the virus of herpes simplex. Various dilutions of serum were mixed with sufficient virus to equal approximately ten minimal lethal doses in each 0.025 cc of mixture (HF strain, mouse brain diluted to  $10^{-4}$ ). After standing for one hour at room temperature each mixture was injected in a dose of 0.025 cc intracerebrally into 3 mice. The results, as shown in the table, demonstrated clearly that the animal acquired antibodies to the virus of herpes simplex during the period of the infection.

#### Neutralization of the Virus of Herpes Simplex (HF Strain)

S indicates that the mouse survived until discarded at two weeks. All tests were made at the same time. Into each of three mice a serum virus mixture was injected. Each number indicates the day after inoculation that a mouse died.

Source of Serum	Dilution of Serum					
	1 2	1 10	1 20	1 40	1 80	1 160
Rabbit K194 at 2 days	333	333	334	333	133	334
Rabbit K194 at 27 days	SSS	SS7	S59	SS7	S55	455
Patient, April 21	SSS	SSS	SSS	SSS	355	445
Patient, 74 days later	SSS	SSS	SS6	SSS	556	S77
15 normal human subjects (pooled serum)	SSS	SSS	SSS	SSS	S57	445

It is known that many, if not most, normal adults have antibodies to herpes virus in their blood stream<sup>23</sup>. It was of interest, therefore, to determine whether this patient had such antibodies. Serum collected at the same time vesicle fluid was obtained for isolation of

<sup>23</sup> Zinnser, H., and Tang, F. J. Immunol. **17** 343, 1929. Andrews, C. H., and Carmichael, E. A. Lancet **1** 857, 1930. Brain, R. T. Brit. J. Exper. Path. **13** 166, 1937. Gildemeister, E., and Ahlfeld, I. Zentralbl. f. Bakt. (Abt. I) **139** 325, 1937. Burnet, F. M., and Lush, D. Lancet **1** 629, 1939.

virus (the third day of the eruption) was found to have antibodies in considerable amount. Serum collected seventy-five days later showed no significant difference in antibody titer. A pool of serum from 15 normal persons contained approximately the same amount of antibodies as this patient's serum.

#### COMMENT

Characteristic infection in rabbits and in mice, the presence of typical inclusion bodies and the development of specific antibodies in an infected rabbit prove that the virus of herpes simplex was present in the vesicles of this patient and presumably caused the eruption. Serum collected from the patient on the third day of the eruption contained antiherpetic antibodies in considerable amount. The titer of these antibodies may have increased during the preceding two days, but there can be little doubt that antibodies were present at the time the eruption began. This is not surprising in view of the known occurrence of ordinary herpetic infections in persons with significant antibody titers in their serum.

It is known that eruptions of the sort commonly called Kaposi's dermatitis may be of a serious nature, and fatal cases have frequently been reported. Whether these severe and sometimes fatal eruptions may be caused by the virus of herpes simplex is not known. If so, there must be a spread of the virus to involve organs other than the skin, a possibility that might reasonably be expected, especially in young children, in view of the ability of this virus to infect many organs and tissues of experimental animals.<sup>24</sup> If true, this fact would be of considerable therapeutic significance. Specific antibodies are capable of interfering with the spread of an established herpetic infection in young mice.<sup>25</sup> Inasmuch as a pool of normal human plasma or serum (see the table) is likely to contain considerable amounts of the specific antibody, the injection of pooled serum or plasma would seem to offer a simple therapeutic measure that might prove to be of real value. It is to be emphasized that such therapy would have a rational basis only in the case of eruptions that might reasonably be considered as caused by the virus of herpes simplex.

#### ABSTRACT OF DISCUSSION

DR. OLIVER S. ORMSBY, Chicago. Much work has been done by several competent observers, most of whom were concerned chiefly in demonstrating the presence or absence of Guarnieri bodies, connecting the disease etiologically with vaccinia. The majority found

<sup>24</sup> Goodpasture, E. W., and Teague, O. J. M. Research **44** 121, 1923. Slavin, B., and Berry, G. P. J. Exper. Med. **78** 321, 1943.

<sup>25</sup> Evans, C. A., Slavin, H. B., and Berry, G. P. J. Bact. **47** 63, 1944.

no such connection. Some observers have concluded that the disease has a pyogenic cause. The clinical picture of Kaposi's varicella eruption and that of Juliusberg's<sup>7</sup> pustulosis vacciniformis acuta are identical, and it is generally accepted that they represent a single disease. Eczema vaccinatum, so well described and discussed by Tedder,<sup>4</sup> resembles the disease under discussion but can be distinguished clinically, as can also the many cases seen in which a pyodermic or impetigenous infection occurs superimposed on an eczema. I have seen a number of these cases in children in whom the secondary pyoderma was extreme but no constitutional symptoms were present. I have also seen extensive herpes simplex in children with no eczematous background in whom no constitutional symptoms occurred. It must be that the growth of the herpes virus on an eczematous skin produces a much more serious reaction, both local and constitutional, in these cases. In 2 patients with Kaposi's varicella eruption the constitutional symptoms were pronounced, the temperature in 1 going up to 106 F. In 1 of these, a man aged 23, hemolytic staphylococci were found in blood cultures, and sulfathiazole was administered for two days before I saw the patient. His leukocytes were reduced to 2,200. The sulfathiazole had no immediate effect on the disease. He was given a blood transfusion and the administration of sulfathiazole was stopped, and in four days the leukocytes had risen to 7,000 and the disease was under control. The condition cleared in three weeks, a typical atopic dermatitis being left. Shortly afterward, I saw a child with a typical eruption implanted on an old eczema (the patient was 13 months of age). The temperature was 103 F, and the leukocytes numbered 8,900. This patient had been successfully vaccinated. It is interesting to note that Wise and Sulzberger (Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1942, p. 151) editorially suggested the herpes virus as the cause. Dr. Lynch's experimental observations appear conclusive as to the etiologic role of the herpes virus in these cases, and I am sure that future investigators will confirm his conclusions.

DR CLINTON W. LANE, St. Louis. In the last eighteen months 5 patients with Kaposi's varicelliform eruption have been observed. Their cases had many resemblances to the cases described by Dr. Lynch, but they exhibited a few differences. The patients varied in age from 6 months to 20 years, and all of them had typical atopic dermatitis. The Kaposi varicelliform eruption began suddenly with fever and cervical adenopathy, the adenopathy was pronounced and was one of the striking features of the disease. Within twenty-four to forty-eight hours an eruption appeared on the face and neck, with rapid extension to other areas. The lesions were vesicles and bullae, most of which were umbilicated. Accompanying the eruption was an actual or relative leukopenia. The course was acute and stormy, and all the patients recovered without sequelae. A virus causation was suspected but was proved for only 1 patient, the fifth in the series. The report of the virologic studies has previously been reported in *Science* by Drs. Blattner and Heys, who proved that the virus is closely related to or is a form of herpes simplex virus. This substantiates the opinion of Dr. Lynch that the disease is not a form of eczema vaccinatum. At variance with the experience of Dr. Lynch was the fact that there was no history of antecedent herpes simplex for any of these patients, nor was there a known contact with herpes simplex in a parent, relative or other persons.

In support of the statement that the sulfonamide compounds were useless was their failure to produce improvement in the 3 patients to whom they were administered. In 1 infant sulfathiazole reduced the white blood cell count to a dangerous level, but on withdrawal of the drug the leukocyte count immediately rose.

In an effort to propose a more appropriate name for this disease without denying to Kaposi the credit for the initial recognition, it is suggested that the disease be known as Kaposi's herpetiform eruption.

COMMANDER MARION B. SULZBERGER (MC), U.S.-N.R. I believe that in the Year Book of Dermatology and Syphilology for 1942 Dr. Wise and I stated that these varicelliform eruptions were not uncommon in our patients with severe atopic dermatitis and expressed the opinion that the disease might have been due to a generalized or rather widespread external inoculation or hematogenous distribution and fixation of herpes virus in the open and scratched areas abounding in these patients. The splendid work reported by Lynch and by others has now confirmed what was previously a mere assumption.

There are many forms of herpes simplex infection in addition to the classic "cold sore" or "fever blister," which can be recognized by all. There is, for example, the recurrent herpetic paronychia and the recurrent bullous herpes simplex of the finger, which often resembles an eczematous eruption or a fixed bullous drug eruption in their recurrence in fixed areas. These were described by the late Wilhelm Frei. There is the follicular and sycosiform herpes simplex of the bearded area, with minute discrete vesicles and/or crusts, often accompanied by severe itching. There is the zosteriform herpes simplex, simulating herpes zoster in its arrangement along the course of nerves. And there is the herpetic stomatitis with its stormy course. In cases such as these, only the modified Paul experiment or other demonstration of the herpes simplex virus will establish the diagnosis.

The knowledge of these variants, as well as the observation that in some of our patients with atopic dermatitis the varicelliform eruption was preceded either by exposure to vaccinia or by exposure to a "fever blister" led us to the conclusion that some instances of Kaposi's eruption were caused by herpes simplex virus. I think that there are milder forms of Kaposi's varicelliform eruption which are not at all uncommon.

One of the lessons which should be learned from Dr. Lynch's excellent study is that there may be other vesicular diseases, now of unknown cause, which are due to herpes virus. In particular, certain common vesicular eruptions of the hands and feet, now usually called "dyshidrosis" or even "eczema," have many features which to me suggest a recurrent herpetic infection. And the same applies to the condition known as nummular eczema. I wonder whether Dr. Lynch or any of the other workers in this field have made a serious attempt to examine these conditions from that point of view.

I think that the word "eczema" should not be used in describing Kaposi's varicelliform eruption. There are already too many confusions surrounding the term "eczema." Why not call this eruption "disseminated herpes simplex," or call it "Kaposi's form of herpes simplex" if one wants to preserve his name?

DR FRANCIS ELLIS, Baltimore. Eczema vaccinatum occurs fairly frequently. I saw 3 cases during the past winter. From what I could tell from the pictures Dr. Lynch showed on the screen, the eruptions looked different from those of my patients, the individual



lesions of which were larger and umbilication was a more prominent feature. The pictures either were not distinct or apparently were taken after involution had set in. In his microscopic picture one could not identify the virus, as several investigators (Ellis, F. A. *Eczema Vaccinatum Its Relation to Generalized Vaccinia*, *J. A. M. A.* **104** 1891 [May 25] 1935, People, A. W., Murrell, T. W., Fowlkes, R. W. *South. M. J.* **35** 667, 1942, and Combes, F. C., and Behrman, *New York State J. Med.*, **43** 2283, 1943) have been able to do, perhaps because the biopsy specimen was not obtained sufficiently early.

Kaposi's varicelliform eruptions apparently may be caused by several different etiologic factors, namely, vaccinia, streptococcal infection (McLachlan, A. D., and Gillespie, M. *Brit. J. Dermat.*, **43** 337, 1936), and now the herpes simplex virus. The herpes simplex virus usually does not cause toxemia, fever and a generalized eruption. The microscopic appearances in tissue of the herpetic and vaccinia virus are so different that there should not be any difficulty in differentiating between them. In the human being the herpes simplex virus does not give immunity. I do not know whether it does in the rabbit. The literature shows that vaccinia does not always give immunity. Gordon (*Brit. J. Dermat.* **48** 525, 1936), C. E. Van Rooyen (*Brit. J. Dermat.* **48** 669, 1936) and Brain and Lewis (*Brit. J. Dermat.* **49** 551, 1937), who aided in the investigation of McLachlan's patients, were unable to conclude that their eruptions were due to a virus.

Dr. Lynch should be complimented on emphasizing that Kaposi's varicelliform eruption may be due to some other etiologic agent. Generalized eruptions may be associated with herpes zoster, but the lesions look like varicella and not like Kaposi's varicelliform eruptions.

DR. M. EBERT, Chicago: I have attempted to demonstrate Guarnieri inclusion bodies in the cytoplasm of the cells in experimental animals and in the lesions of the patient himself always with failure. I never thought about herpes. I have studied the cases of 3 patients, 2 children and 1 adult, in an attempt to demonstrate vaccinia virus. All were failures. There were no Guarnieri bodies, either in the tissue of the patient or in the experimental animal. And the 2 young children were afterward successfully vaccinated, which means something, I believe, because such a violent reaction to vaccinia virus should produce an immunity for at least some time.

Recently, through the courtesy of Dr. Zinnes, I saw a patient with an eruption of this type in the Illinois Research Hospital, a young woman whose condition was much more severe than that of any of those that Dr. Lynch mentioned and more like the ones described by the last speaker. This patient was acutely ill, had a high fever and had crops of lesions that certainly resembled variola. Material was taken from the lesions, and attempts were made to demonstrate elementary bodies. This was impossible, largely, I think, on account of the secondary infection and the fact that the material was taken a little too late. It must be taken at exactly the right time, when the vesicle contents still are clear. Then inoculation on rabbits' eyes was successful, producing violent keratitis, which I ascribed, unfortunately, to secondary infection.

On going over the sections again after I had heard Dr. Lynch's paper, I found that the typical inclusion

bodies which are found in the herpes group, (that is, in herpes zoster, in herpes simplex and in chickenpox) were found not only in the rabbit's eye where the material had been transmitted experimentally but in the lesions taken from the skin of the patient himself. So this would limit, I believe, as far as is known now about inclusion bodies, the disease to one of those three.

I disagree with some of the other speakers that a primary herpes infection does not produce a violent illness or high temperature. In his review of the herpes virus about twenty years ago, Doeir, a Swiss investigator, mentioned the fact that in Europe it was not infrequent to see persons with what was called "herpetiform fever," an initial attack of a very violent herpetic eruption associated with high temperature, malaise and headaches in a person who had never before suffered from herpes simplex.

DR. FRANCIS W. LYNCH, St. Paul: Dr. Ormsby pointed out that the general symptoms are more severe and the white blood cell count less elevated than might be expected with the degree of fever and extent of the eruption, respectively. These characteristics are also observed frequently in other diseases caused by viruses (e. g., influenza).

The presence of lymphadenopathy was not recorded by Kaposi, but, as Dr. Lane indicated, it is frequently present and in severe forms of the disease it may be a striking feature. I do not believe that extensive lymphadenopathy or the presence of pustules need be expected in all cases, milder examples of the disease are probably more common than severe ones, and in such cases only tense vesicles may be present, many of them never developing even to the stage of umbilication. As Dr. Ebert pointed out, the first inoculation with the virus of herpes simplex often produces a more severe reaction than does reinoculation. This probably explains to some extent the fact that this disease is more severe in infants and small children, who have probably not previously been exposed to the virus.

As suggested by Dr. Sulzberger, herpes simplex is often more important than a simple "cold sore," and clinical variations are numerous. One variant, "herpetic fever," was mentioned also by Dr. Ebert. It is given extensive discussion by Schonfeld in Jadassohn's "Handbuch."

It is unlikely that biopsy will be frequently applied as a diagnostic procedure in cases of this disease, yet it might be of greater assistance than the remarks of Dr. Ellis suggest. With this aid one can easily distinguish viral infection from ordinary eczema or its pyogenic complications. It is more difficult to distinguish between eczema vaccinatum and herpetic complications of eczema.

Dr. Ebert has been particularly interested in studies with viruses, and his discussion and that of Dr. Sulzberger suggest how difficult are experimental studies in that field. Negative experimental evidence is of little significance. Demonstration of the virus usually requires study of an unruptured vesicle, preferably not over one or two days old. For these reasons it is likely that the diagnosis of herpetic complication of eczema will usually be made on a clinical basis. The pathogenesis seems to be well established, and it is now only necessary for clinicians to become familiar with the disease.



## Clinical Notes

### SULFAPYRIDINE AS A HEMOSTATIC AGENT

C. RUSSELL ANDERSON, M.D., LOS ANGELES

In 1942 Cunningham<sup>1</sup> reported on the use of sulfapyridine as a hemostatic agent. He found that after sulfamethylthiazole powder had been instilled into the operative wound after radical external frontal sinusotomy for osteomyelitis of the frontal bone the usual considerable postoperative oozing was absent. This observation led him to experiments on guinea pigs. Circular wounds were made on the backs of the animals, and five to seven days later the scabs were evulsed so that an open granulating and freely oozing surface remained. Powdered sulfapyridine, sulfanilamide, sulfathiazole, sulfamethylthiazole<sup>2</sup> and talc were sprayed on with a powder blower. The wounds treated with sulfamethylthiazole and sulfapyridine exhibited an immediate tendency to hemostasis, while the wounds treated with the other powders and with talc and untreated control wounds all oozed for from five to ten minutes. The sulfapyridine powder was also found to be bacteriostatic. The results of this experimental work led Cunningham to use sulfapyridine for the control of the troublesome postoperative secondary tonsillar hemorrhage, with uniformly excellent results. He also successfully employed sulfapyridine powder by insufflation in the control of persistent bleeding in a case of bronchial erosion. He suggested that the drug might be of value when locally applied to superficial abrasions, such as brush burns.

Cunningham's report led me to use sulfapyridine powder locally in treatment of a number of diseases. Following are 3 illustrative cases.

#### REPORT OF CASES

CASE 1—H. A. B., a white man aged 28, presented a severe telangiectatic rosacea of the tip of the nose.

1. Cunningham, B. P. *Clinical and Experimental Studies with Sulfapyridine as a Hemostatic Agent*, in *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1943, vol. 34, p. 12.

2. Since sulfamethylthiazole was found by various investigators to produce toxic effects, it is no longer available on the market.

About half of the vessels were removed by scarification with an electrosurgical cutting current. This was followed by a persistent oozing for five hours. Sulfapyridine powder was unobtainable from any source on that day. Ten weeks later, after persuasion, he permitted the remaining vessels to be treated with a cutting current. Again a persistent oozing ensued, which ceased instantaneously after application of sulfapyridine powder.

CASE 2—S. K., a white woman aged 68, presented an oozing granulating lesion 1 cm. in diameter of the lower lip. Two weeks earlier a keratosis had been removed from the lower lip by her physician. This was followed by a persistent uncontrolled slow bleeding. When I saw her she was panic stricken and exhausted from loss of sleep. The oozing ceased immediately after application of sulfapyridine powder and healing proceeded uneventfully.

CASE 3—H. W., a white man aged 65, presented a large pyogenic granuloma of the right forearm. This was removed with a Post cautery. As is sometimes the case after removal of a pyogenic granuloma of large size, persistent oozing occurred which was easily controlled by the application of sulfapyridine powder.

#### COMMENT

The local application of sulfapyridine powder to wounds after removal of lesions by electrodesiccation, cutting current or cautery is especially useful in producing hemostasis. The surface of the wounds becomes hard and dry, and the wounds heal without infection. The use of sulfapyridine powder is superior to a solution of gentian violet medicinal, which is often used.

#### CONCLUSION

The local application of sulfapyridine powder to produce hemostasis is extremely satisfactory and deserves wider use.

1930 Wilshire Boulevard

# Abstracts from Current Literature

EDITED BY DR HERBERT RATTNER

THE "LUPUS ERYTHEMATOSUS" CONCEPT AN ATTEMPT AT INTEGRATION JOHN H STOKES, HERMAN BEERMAN and NORMAN R INGRAHAM, Am J M Sc 207 540 (April) 1944

Stokes and his associates attempt to summarize and clarify recent suggestions as to the nature, cause and cure of lupus erythematosus. They look at the disease in the light of allergic reactions to infection, regarding the chronic discoid form as related to the follicular "ids" and the systemic form as an expression of vascular injury and allergy. They note the reports of observers who regard the cellular and connective tissue changes as manifestations of allergy but point out that there is not as yet a general acceptance of colloid degeneration as a sign of allergic reaction. Discoid lupus erythematosus can be hypothetically accounted for as follicular (seborrheic) infection plus allergic reaction to that infection (yeasts and staphylococci).

Dissemination of a discoid or follicular erythematous lupus with the appearance of desquamative patches with follicular atrophy over other parts of the body is simply an extension of the follicular "id" beyond its conventional locus, under conditions affecting the general allergic state of the individual. On the other hand, the reaction that underlies the chronic discoid process may at a suitable provocation pass over into the field of vasculoallergic manifestations and assume the far graver characteristics of the so-called acute disseminating type of the disease. The authors state that as to the nature of the infection to which allergy develops or exists no absolute decision can be had at this time and the contribution of a concept of infection-allergy to the treatment of lupus erythematosus is largely negative. They regard therapy with bismuth as equally effective as and safer than treatment with gold. They warn that sulfonamide compounds must be used with the utmost caution, though they are helpful in some cases.

Reviewing the suggestions of others, that lupus erythematosus may be subject to endocrine influences, they state that "it would appear justifiable to undertake further study of possible relationships between gonadal hormones and lupus erythematosus and to investigate the possible usefulness of castration in female patients more extensively."

LYNCH, St Paul

CANCER ASSOCIATED WITH ACANTHOSIS NIGRICANS REVIEW OF LITERATURE AND REPORT OF A CASE OF ACANTHOSIS NIGRICANS WITH CANCER OF THE BREAST HELEN OLLENDORFF CURTH, Arch Surg 47 517 (Dec) 1943

The case of a 47 year old woman who had cancer of the right breast and acanthosis nigricans is presented. After removal of the breast the acanthosis nigricans tended to subside for a while. The patient died about one and one-half years after operation. Permission for opening of the thoracic cavity was not given. Widespread metastases were found in the liver, left kidney and left adrenal gland. Acanthosis nigricans had reappeared a few months after operation and had spread over wide areas of the body.

This is the ninth case of mammary cancer associated with acanthosis nigricans. The high malignancy of this tumor corresponds with the character seen in all carcinomas accompanying acanthosis nigricans. A complete review of all cases published is given, and all tumors accompanying acanthosis nigricans are tabulated.

Benign and malignant acanthosis nigricans are identical. Instances in which characteristics of the benign and of the malignant types were shown successively or simultaneously are presented. The presence of acanthosis nigricans and cancer in the same patient is not coincidental, since (1) the percentage of cancer in patients with acanthosis nigricans is extremely high, (2) the two diseases become manifest at about the same time and run a parallel course, and (3) many young persons suffer from cancer and acanthosis nigricans.

Previous concepts of the causation of acanthosis nigricans, such as those attributing it to disturbances of the sympathetic nervous system or of the adrenals or other endocrine glands, should be discounted and cancer considered the essential etiologic factor of the disease. In cases of malignant acanthosis nigricans some properties of the tumor may activate the cutaneous lesions. In the benign type the same role of activation seems to be played by one of the sex hormones. There are a large number of cases of benign acanthosis nigricans on record in which the disease appeared or began to spread at puberty. The role of cancer in the family history of patients with acanthosis nigricans, the type of cancers that have been associated with it and the chronologic independence of acanthosis nigricans and cancer speak for a genetic relationship between the two diseases. Criteria of benign and malignant acanthosis nigricans are given. CURTH, New York

OCULAR ROSACEA G WISE, Am J Ophth 26 591 (June) 1943

The present study of rosacea was undertaken primarily to evaluate the various etiologic possibilities, in particular the theory that rosacea is due to riboflavin deficiency. The following conclusions are reached.

"Ocular rosacea occurs following facial rosacea and both are manifestations of the same disease."

"At present the fundamental cause of rosacea is unknown."

"Rosacea is not a manifestation of riboflavin deficiency."

"Previously considered causes of rosacea, such as gastrointestinal disturbances, focal infection, endocrine and other disorders, are not fundamental etiologically, but in some cases may be transient aggravating factors."

"Rosacea probably does not occur in the Negro race."

"Lowered gastric acidity is neither specific for rosacea nor nearly so frequent an accompaniment of it as has previously been thought. Its presence is of no special significance."

"Hyaluronic [acid] ester is not decreased in the cornea of the rat that has become vascularized due to riboflavin deficiency."

"The importance of secondary infection in cases of ocular rosacea has been neglected in the past

"Except in the unusual and rare cases of severe ocular rosacea without secondary infection, most of the distressing symptoms and sequelae of ocular rosacea are due to secondary infection with staphylococci

"The secondary infection in ocular rosacea can be controlled in almost all cases with 5 per cent sulfathiazole or sulfadiazine ointment, used locally several times daily

"Rosacea probably is due to some factor causing vasodilatation in the facial area"

W ZLNTMAYER [ARCH OPHTH]

RAT-BITE FEVER COMPARISON OF THE SPIROCHETAL (SODOKU) AND BACILLARY (HAVERHILL FEVER) FORMS C MICHAEL WITZBERGER and HERBERT G COHEN, Arch Pediat 61 123 (March) 1944

Witzberger and Cohen feel that in this period of global transportation physicians should acquaint themselves with the two clinical syndromes of rat bite fever. Sodoku is caused by *Spirochaeta morsus muris*, and Haverhill fever is due to *Streptobacillus moniliformis*. The authors have prepared a short table showing a comparison of these two syndromes which may serve as an aid in differential diagnosis. The two syndromes are discussed separately, and a case of each variety is presented. In the sodoku form a chancre-like ulceration develops at the site of the bite, which is followed by regional lymphadenitis and later by a generalized maculopapular rash which fades during the afebrile periods. In the Haverhill form there is no subsequent induration at the site of the bite and the eruption is at first macular and later petechial. In this form there develops a metastatic arthritis as a result of generalized septicemia.

GELBER, Los Angeles

TREATMENT OF ACNE VULGARIS CHARLES H BIRNBERG and CHARLES R REIN, J Clin Endocrinol 4 65 (Feb) 1944

Birnberg and Rein report definite improvement of acne in 14 of 17 patients treated by injections of serum from pregnant mares. Six of these patients showed hirsutism which was not altered by treatment, and 2 gave abnormal results on hormonal studies. Most of them presented evidence of some degree of hypopituitarism, and all of them had some associated menstrual disturbance. The authors do not infer that pregnant mare serum is a cure for acne vulgaris, but they suggest that in any case in which the disease is influenced by the menstrual cycle there should be thorough endocrine study and treatment should be instituted according to the results of this study.

LYNCH, St Paul

THE VELOCITIES OF INHIBITION OF BACTERIAL GROWTH BY SULFONAMIDE AND OF THE ANTAGONISTIC EFFECT BY P-AMINOBENZOIC ACID JULIUS HIRSCH, J Immunol 48 199 (March) 1944

According to Fildes' theory, the effect of sulfonamides is based on the structural similarity with paraaminobenzoic acid. Paraaminobenzoic acid (an "essential metabolite") and sulfonamide compounds compete with each other at sites within the cells important for the process of multiplication. According to this theory, inhibition of growth by sulfonamide compounds and the reversal of this inhibition by paraaminobenzoic acid must both represent reversible reactions.

On the basis of the results of his experiments, the author believes that the interference with the action of paraaminobenzoic acid by sulfonamide compounds postulated by Fildes and the experimentally demonstrable interference with the sulfonamide effect by paraaminobenzoic acid cannot be considered as equivalent processes caused by a similar reversible reaction. This becomes the more evident he thinks, if the concentrations of the participating substances are considered. He found that inhibition of growth is instantly antagonized by a concentration ratio of 1 mol of paraaminobenzoic acid to 10 mols of Irgafen (Gergy 867, N<sub>1</sub>-3,4-dimethylbenzoylsulfanilamide). He could make no definite statements concerning the concentration ratios of the two competitors in an inhibitive experiment. If paraaminobenzoic acid is produced at all in a synthetic medium, the concentration is certainly several powers of 10 less than the concentration of N<sub>1</sub>-3,4-dimethylbenzoylsulfanilamide which, however, acts only very slowly regardless of the quantitative advantage. His findings suggest that the inhibition of bacterial proliferation by sulfonamide compounds is a more complex process than the reversal of inhibition by paraaminobenzoic acid. The inhibiting effect of sulfonamide has a lag period of one to two hours, in contrast to this, the bacteriostatic effect of sulfonamide compounds is instantly antagonized by addition of paraaminobenzoic acid.

THE ACTION OF DETERGENTS ON STAPHYLOCOCCAL INFECTIONS OF THE CHORIO-ALLANTOIS OF THE CHICK EMBRYO T W GREFF, J Infect Dis 74 37 (Jan-Feb) 1944

The widespread interest in the antibacterial effects of detergents is evident from the increasing number of publications dealing with their action. Some authors have found that the bacteriostatic and germicidal action of the cationic detergents is much greater than that of the anionic agents. Because of these observations the author made a study of the comparative therapeutic action of these two classes of detergents, using the chick embryo technic, which has proved successful for the in vivo testing of various therapeutic agents.

He found that none of the anionic agents were therapeutically active while most of the cationic agents exerted a demonstrable therapeutic effect. Replacement of the chloride or bromide ion by the iodide ion in several compounds resulted in a lower degree of therapeutic activity. Variation in the length of the carbon chain (12 to 18) in the alkyl groups of a homologous series of compounds resulted in no great changes in therapeutic effectiveness. Because several compounds similar in structure and degree of germicidal action exhibited great differences in effectiveness in the egg, the author concluded that the degree of germicidal action of a compound is not a sound basis for prediction of relative therapeutic effectiveness even within such a restricted group as the cationic detergents. He feels that the utility of the infected chick embryo as an adjunct in the evaluation of disinfectants is well demonstrated by his experiments.

CORNBLLIT Chicago

A STUDY OF OILS USED FOR INTRAMUSCULAR INJECTIONS. A STUDY OF THE PHYSICAL, CHEMICAL AND BIOLOGIC FACTORS WILLIS E BROWN VIOLLET M WILDER and PAULINE SCHWARTZ, J Lab & Clin Med 29 259 (March) 1944

The authors undertook to investigate the factors which should guide a physician in the selection of the oil vehicle for intramuscular injections.

The suggested criteria for the ideal oil included physical, chemical and biologic specifications, which are 1 Chemically the oil should be stable and neutral in reaction and should not react with medication to form toxic products 2 Biologically it should be inert and nonirritating It should be essentially free of antigenic properties and be rapidly absorbed from living tissue, leaving no residue 3 Physically it should be a good solvent or dispensing medium and not too viscous to pass readily through the needle Extremes in temperature should not alter any of these features

Using these criteria, they studied four commonly used oils (corn, peanut, sesame and cottonseed) The antigenic study was made on 20 patients who received at weekly intervals two injections of each of the four oils Approximately two months later these patients were tested by the patch and intracutaneous tests The biologic reaction was investigated by injecting the oils intramuscularly into the large muscles of the extremities of rats and rabbits The muscular reactions were studied microscopically by means of frozen and stained sections The intensity of the reaction was judged by (a) the accumulation of leukocytes, (b) the formation of oil cysts, and (c) the deposition of fibrin They found that sesame and corn oils are superior to peanut and cottonseed oils for intramuscular injections, for they are (1) more suitable physically and chemically for this purpose, (2) more quickly absorbed from the tissue, (3) less antigenic, and (4) less irritating to tissue

GELBER, Los Angeles

SKIN DISEASE OF THE NEWBORN INFANT MACHTELD  
E SANO, J Pediat 23 280 (Sept) 1943

As a result of an intensive study of a case of desquamative erythroderma (Leiner's disease) correlated with an extensive review of the literature, the author concludes that the underlying cause of desquamative erythroderma (Leiner's disease) and exfoliative dermatitis (Ritter's disease) is a temporary dysfunction of the endocrine system The dysfunction in the majority of infants probably originates in the mother, who has to adapt herself physiologically to the demands put on her endocrine system during pregnancy

The histologic examination of the endocrine glands, illustrated by photomicrographs, and biochemical studies of the case confirm some of the observations reported in the literature

The conditions observed in this detailed clinical and histopathologic study indicate that desquamative erythroderma cannot be considered as an entity but that it is rather as a manifestation of an underlying cause responsible also for exfoliative dermatitis and possibly other cutaneous diseases in the newborn infant

SONTAG, Yellow Springs, Ohio  
[AM J DIS CHILD]

FAVUS IN MASSACHUSETTS A REPORT OF TWO CASES  
G E MORRIS, New England J Med 230 667  
(June 1) 1944

Morris reports 2 cases of favus, in 1 the patient was a 17 year old girl and in the other an 18 year old girl In both of them direct examination and cultures revealed *Achorion schoenleini*, also demonstrated by the characteristic fluorescence under the Wood light

Because of the usual therapeutic difficulty and the known recurrences even after roentgen epilation, Morris used a solution of 10 per cent thymol in chloroform, twice daily, a shampoo twice weekly and manual epila-

tion at home and once weekly at the clinic under the Wood light

One year of such treatment has been successful in both cases

ECZEMA VACCINATUM F C COMBES and H T BEHRMAN, New York State J Med 43 2283, 1943

Combes and Behrman report a case of eczema vaccinatum which developed on the face of a 24 year old man with chronic folliculitis of the beard after contact with recently vaccinated members of the family The danger of vaccination in the presence of a cutaneous disease is emphasized

CUTANEOUS MANIFESTATIONS OF TUBERCULOSIS A C  
CIPOLLARO, New York State J Med 44 1557, 1944

Tuberculosis of the skin is divided in two main groups, the localized and the hematogenous Etiology, clinical appearance and therapy are discussed for the various types

RONCHESI, Providence R I

MONILIASIS OF THE EXTERNAL EAR CANAL WILLIAM  
L DOBES, South M J 36 614 (Sept) 1943

Dobes calls attention to the work that has been done and the progress made in attempts to separate and classify the saprophytic and the pathogenic fungi The yeastlike fungi most frequently encountered are (1) *Monilia*, (2) *Cryptococcus* and (3) *Mycoderma* *Monilia* is subdivided into several strains, of which *Monilia albicans* is considered pathogenic, while the other strains are considered saprophytic In reviewing the current literature the author found only two articles in which reference was made to involvement of the external canal by *M albicans* He reports a case of disease of the external canal due to *M albicans* The patient was treated with a 2 per cent solution of methylosaniline (gentian violet) at daily intervals, and the lesion was healed within ten days Local applications of 1 per cent mercury bichloride in 50 per cent alcohol and of mercurous iodide in alcohol are sometimes used in treating this type of infection

SINGITON, Dallas, Texas [ARCH OTOLARYNG]

A PLEA FOR THE STANDARDIZATION OF THE LEPRONIN  
TEST JOHN W FIELDING and ROBERT G  
COCHRAN, M J Australia 1 313 (April 8) 1944

The active element for the lepromin test is contained in the bacillary content of the emulsions Effective prolonged grinding for the separation of bacilli from tissue element is all important Standardization of the bacillary content of the emulsions is essential in order to obtain uniform reactions The Breed milk count (bacteria) is advocated when emulsions of a low bacillary content are to be standardized A combined Breed-Owen count method may be used for emulsions of low or high bacillary content When used by the authors the Breed-Owen count has given reasonable satisfaction

THE TREATMENT OF CARCINOMA OF THE DORSUM OF  
THE HAND P D BRADDON, M J Australia 1 368  
(April 22) 1944

Early epitheliomas of the dorsum of the hand are almost invariably of the squamous cell variety In some thousands of cases only 6 instances of basal cell epitheliomas were encountered This type of lesion, up to a little over 2 cm in diameter, is best treated surgically

Advanced epitheliomas are growths over 2 cm in diameter. Two hundred patients with advanced epitheliomas were treated by radon molds with consistently excellent results. In the treatment of this lesion, radium or radon needles or seeds should never be implanted. The dose delivered is always 6,000 r over a minimum period of ten days and a maximum period of sixteen days.

**CREeping ERUPTION (LARVA MIGRANS)** JAMES F HUGHES, M J Australia 1 393 (April 29) 1944

Hughes reports 2 cases of larva migrans. He has found three forms of treatment reliable. Excision of the migrating larva, refrigeration with ethyl chloride spray for two minutes and application of solid carbon dioxide were effective procedures.

**THE USE OF THE CHORIO-ALLANTOIS OF THE DEVELOPING CHICK EMBRYO IN THE DIAGNOSIS OF SMALL-POX** E A NORTH, J A BROBEN and A H MENGONI, M J Australia 1 437 (May 13) 1944

By the use of the developing egg as a medium, variola and vaccinia viruses may be distinguished. In addition to its greater sensitivity compared with the rabbit's cornea, the developing chick membrane permits differentiation of variola and vaccinia, whereas a positive reaction to the Paul test is given by both variola and vaccinia viruses. The appearance of the foci produced on the chorioallantois enables distinction to be made between variola virus and the strains of vaccinia virus.

**THE LEFROMIN TEST IN LABORATORY ANIMALS** J W FIELDING, M J Australia 1 439 (May 13) 1944

The lepromin test in animals gave a variable result except in the case of rats, which consistently failed to react. This was true with emulsions both from human beings and from rats.

HENSCHEL, Denver

**TREATMENT OF SCABIES WITH AN EMULSION OF ROTENONE** E P WOODROW, South African M J 17 233 (Aug 14) 1943

The author reports excellent results in the treatment of 225 patients with scabies with an emulsion of rotenone. Of the 177 patients who returned for observation, all except 10 were cured by one course of treatment. Of the 10 who relapsed, 9 were cured after one further course of treatment and the tenth required a third course. The solution used on all infants under 9 months of age and on many adults with mild infestations consisted of 1 per cent rotenone and 3 per cent chloroform in mucilage of chondrus. For severe infestations in adults the percentages of rotenone and chloroform were doubled. The lotion was applied twice the first day and twice the second, a bath being taken before the initial application but not again until the third day.

GONCE, Madison, Wis [AM J DIS CHILD]

**EAGLE'S FLOCCULATION TEST OF THE SPINAL FLUID** JOÃO BAPTISTA DOS REIS and WALDEMAN CARDOSO, Arq assist psicopat estad São Paulo 7 207 (March-June) 1942

The authors used the Eagle flocculation test in 100 cases of neurosyphilis. In cases of nontreated neurosyphilis the Eagle flocculation and the Wassermann test were equally sensitive. In cases of old, unsuccessfully treated neurosyphilis the Eagle test appeared to be more sensitive than the Wassermann test. In cases in which the disease was under treatment there was a significant parallelism between the Eagle and the Wassermann test. The results of the Wassermann and of the Eagle test were in disagreement in only 7 of 40 cases.

SAVITSKY, New York [ARCH NEUROL & PSYCHIAT]

## Society Transactions

### MANHATTAN DERMATOLOGIC SOCIETY

ANTHONY C. CIPOLLARO, M.D., *President*

WILBERT SACHS, M.D., *Secretary*

Jan 11, 1944

#### Elephantiasis of the Scrotum and Left Leg Five Year Use of Sulfonamide Compounds Presented by DR. E. WILLIAM ABRAMOWITZ

I R., a 58 year old merchant born in Hungary and married, has three children alive and well. He has been in the United States for forty-two years. There is no history of any abnormalities in his family. When he was 12 years old and living near Budapest, an enlargement developed on the left side of his scrotum. In 1903 he was operated on at Mount Sinai Hospital, in New York city, for enlargement of the right side of the scrotum. He made a stormy recovery.

In 1922 the patient noted the development of an oozing dermatitis of the scrotum, which was rather persistent. In 1925 he made a one month trip to Louisiana, South Carolina, Alabama and Tennessee. The dermatitis became aggravated in 1932, accompanied by fever and chills and a definite increase in the size of the scrotum. After that he had on the average four attacks of fever (temperature 103 to 104 F) a year, which lasted about three or four days. The swelling of the scrotum continued to increase, and in 1939 swelling of the left leg began to develop.

In 1939 he began to take five tablets of sulfanilamide daily for three or four days during the febrile attacks, which recurred about every five to six weeks. He was referred to me in April 1941, and I prescribed azosulfamide and later sulfathiazole instead of sulfanilamide.

There is a tremendous enlargement of the scrotum, which presents a reddened, thin skin. It measures 20 by 12 inches (50 by 30 cm). The skin of the penis is swollen, and the glans is retracted. Pitting is present in these areas as well as on the left leg. There is no dermatitis of the leg.

The patient had a 4 plus reaction to staphylococcus toxoid, and a 1 plus reaction to hemolyticus and viridans streptococci. At one time there was a slight trace of sugar in his urine, but this has since disappeared. Examination of the blood for filariae was unsuccessful.

Besides the sulfathiazole, the patient received fractional roentgen ray therapy and injections of staphylococcus modified toxoid. Under this treatment no febrile or scrotal reactions recurred from April 1941 until August 15 of that year, and they occurred then because the use of sulfathiazole had been discontinued. There were no symptoms from August 1941 until May 1942, when he stopped taking the drug for about three or four months. A relapse developed in December 1942, at which time he had discontinued the drug for one year. Another attack occurred in February 1943. Then he began to take the drug and vaccine again. In October 1943 he once more stopped taking the drug, and another attack developed in December 1943.

The roentgen therapy and the staphylococcus toxoid (when given without the sulfathiazole) did not prevent

recurrences. Further tests for filariae will be made, and surgical consultation is advised regarding operation to relieve the difficulty in urination caused by the retraction of the penis and also to reduce the size of the scrotum.

#### DISCUSSION

DR. MAX SCHEER: Filariasis is occasionally seen in temperate climates. I think that an examination of the blood for filariae should be repeated, especially at night. I doubt if the disease is present, but it should be excluded.

DR. HERMAN SHARLIT: If there is no blood infection behind this disability, why cannot some plastic operation be performed to make the patient comfortable?

DR. JOSEPH R. RICCHIUTI (by invitation): I have seen a good many patients with filariasis coming back from the southwest Pacific. They have lost most of the elephantiasis after their return to the States, only fibrosis remaining. In none of them have I been able to find filariae. Associated with the infection one frequently sees a recurrent generalized urticaria.

DR. FRED WISF: I would like to inquire from the members whether this type of case is favorable for operative procedure.

DR. E. WILLIAM ABRAMOWITZ: The Kondoleon operation removes tissue down to the fascia of the muscles in elephantiasis of the legs. The disease has a tendency to recur, however, and subsequent operation may be necessary. The recent literature indicates that patients affected with filariasis may carry the organisms in the blood without symptoms and without blockage. It is not the filariae alone that cause the trouble, apparently, but the attacks of lymphangitis due to secondary invaders which also appear in cases without filariae. One has to keep on testing for filariae, not only at night and not only in the blood but in aspirated lymph tissue. I am against the indiscriminate administration of the sulfonamide drugs, but here is a patient who cannot get along without them and who has taken them for five years without any trouble—sulfanilamide, azosulfamide, sulfathiazole, sulfapyridine and sulfadiazine.

#### A Case for Diagnosis (Pemphigus?) Presented by DR. E. WILLIAM ABRAMOWITZ

Lieutenant A. J., aged 23, had an ulcer on the buccal surface of the lower lip in June 1941. The lesion was treated with silver nitrate and healed in one week. Shortly after this, however, new ulcers appeared in the mouth, on the tongue and on the soft palate. The lesions were painful, they lasted about seven days, healed and were followed by a new crop. Six months later, in January 1943, the ulcers began to appear in the mouth as bullae and followed the same course. Because a smear showed Vincent's bacilli, two partially impacted wisdom teeth were extracted. In September 1943, a small vesicle containing clear fluid appeared on the normal skin of the right thigh. A similar vesicle appeared on the left shoulder one month later. During the next four months crops of vesicles and bullae appeared on the face, shoulders and wrist. The patient



states that itching precedes the appearance of a vesicle. Recently he noticed that his nose contained a bloody crust. Examination showed a nasal perforation with ulceration of the mucous membrane surrounding this site.

Exhaustive studies concerning intake of drugs showed that the patient occasionally took acetylsalicylic acid, Ex-Lax and phenobarbital. He used Squibb's tooth paste (pink) and occasionally drank Chianti wine. A test dose of phenolphthalein produced large bullous lesions with surrounding erythema on the glans penis within twenty-four hours. There was no exacerbation of the oral lesions.

In July 1943, an apical abscess was found in a lateral incisor tooth which was extracted; culture showed *Streptococcus viridans*.

On Jan 19, 1944 there was a sudden appearance of numerous pruritic pea-sized erythematous macules on the palms.

The general physical examination gave normal results except for the skin. On the face, right shoulder and left wrist there are a number of healing ulcerations. There are several tiny vesicles on the soft palate. There are pea-sized erythematous macular lesions on the palms. There has been no loss of weight.

Results of urinalysis and a blood count were normal, and the Kahn reaction was negative. A patch test with 30 per cent solution of potassium iodide elicited a negative reaction. The calcium content of the blood was 114 mg per hundred cubic centimeters, and the phosphorus content was 42 mg. A smear from vesicle fluid showed many polymorphonuclear cells but no eosinophils, and culture showed a *Streptococcus viridans*.

Histologic examination showed the vessels of the middle and upper parts of the cutis to be dilated, many being filled with blood elements. There was some edema of the vessel walls and swelling of the intima and some disruption of the vessel walls in places. About the vessels was also a moderate small round cell and wandering connective tissue cell infiltration with many polymorphonuclear leukocytes. Within the epidermis was a tremendous cavity filled with polymorphonuclear leukocytes, many of which were eosinophils. The diagnosis was pemphigus.

The treatment so far has been to eliminate all drugs. The patient is taking 100,000 U S P units of vitamin A and 200,000 U S P units of vitamin D daily. He has had fewer lesions in the last two weeks.

NOTE—The patient remained clear of lesions for six weeks and was then given a therapeutic trial of phenolphthalein, acetylsalicylic acid and acetophenetidin. No new lesions resulted. There has been a three month interval of freedom from lesions.

#### DISCUSSION

DR FRED WISE. I do not think that these are sufficient clinical changes to justify the diagnosis of pemphigus vulgaris in this patient.

DR ISADORE ROSEN. In view of the facts that the patient had similar lesions a year and a half ago, that there is a history of appearance and disappearance of lesions and that there are lesions on the palms, I think that he is suffering from erythema multiforme and not pemphigus. Pemphigus is usually a progressive disease and does not show periods of spontaneous remission as in this case.

DR WILBERT SACHS. I examined the sections in this case, and to me there is presented a picture of pemphigus. It is a typical intraepidermic bullous lesion, which to me would be against a diagnosis of drug eruption or any other type of erythema multi-

forme. The epidermis was split, and there were some eosinophils in the bullous lesions, the character of the vessels underneath also suggested pemphigus.

DR FRED WISE. Tense bullae may appear in pemphigus, but I do not recall the occurrence of macular lesions of the palms in that disease.

DR HERMAN SHARIT. If there is a question of the patient's having reacted to phenolphthalein once, that should be verified. If this is true, it is fair to assume that even if the eruption is not due to phenolphthalein it is due to some process that is not pemphigus.

DR JOSEPH F. RICCHIUTI (by invitation). The macular lesions on the palms appeared tonight, and I saw them for the first time at 7 p. m. Dr Abramowitz and I have been reluctant to accept a diagnosis of pemphigus, having thought of erythema multiforme of the bullous type, and it is only our studies, the lack of a history of drug ingestion, the histologic examination and the recurrence of the lesions that have led us to that opinion. I still feel there is a possibility of a toxic erythema of the bullous type.

DR MAURICE J. COSTELLO. Has the Pels-Marchet phytopharmacologic test been performed?

DR JOSEPH F. RICCHIUTI. No.

DR E. WILLIAM ABRAMOWITZ. My opinion just now is that the diagnosis is undecided, but I do not think the patient has pemphigus.

#### Eosinophilic Granuloma Presented by DR GEORGE M. LEWIS

M. R., a man aged 47, was previously presented before the Manhattan Dermatologic Society, on Oct 13, 1942, and before the New York Academy of Medicine, Section of Dermatology and Syphilis, on May 3, 1943.

#### DISCUSSION

DR FRED WISE. An Italian dermatologist presented two articles on eosinophilic tumor formation under the name of granuloma eosinophilicum. Dr Lewis tells me that he is acquainted with the articles but that this patient's lesions are not identical with those described.

DR JACK WOLF. Eosinophilic tumors of bone have also been described. It might be advisable to make roentgenograms of the long bones and to perform sternal puncture.

DR E. WILLIAM ABRAMOWITZ. I should like to offer a diagnosis of an unusual form of mycosis fungoides. I think that cases have been described which present little else but eosinophilic tumors.

DR WILBERT SACHS. I have never seen a slide in which there were pure eosinophils in the tissue. I should assume, however, that in such cases, whether the tumors arise in the bone or in the skin, they would be related more to some form of leukemia or mycosis fungoides than to any other disease with which I am acquainted.

DR GEORGE M. LEWIS. I have followed this man carefully for several years without establishing any primary focus for the eruption. His blood picture is not abnormal except for a slight increase in the eosinophils. It might be good procedure to carry out Dr Wolf's suggestion. Regarding the possibility of mycosis fungoides, the tumors are not radiosensitive, and the lesions develop and disappear in a manner different from those of mycosis fungoides. Dissolution occurs usually by softening of the lesions, and then they entirely disappear within a week.

### Exudative Discoid and Lichenoid Chronic Dermatitis Presented by DR MAURICE J COSTELLO

B K, a salesman aged 43, was examined by me in July 1941, at which time he stated that he had had a pruritic eruption for six months, during which period he had lost 10 pounds (4.5 Kg). There is no history of personal or familial hypersensitivity. The eruption began on the anterior aspect of the left leg and later became generalized, appearing on the inner aspect of the arms, sides of the chest, buttocks, scrotum and thighs. He was admitted to Lenox Hill Hospital at that time, where he was given a series of intravenous injections of typhoid vaccine. Coal tar paste was applied. He improved during his stay in the hospital but was not completely cured when discharged.

Since that time the patient has received occasional low voltage roentgen ray treatments, with temporary relief. In addition, sedatives, such as sodium amytal and tablets of three bromides N F, have been necessary to relieve the intense pruritus. Exposure to sunlight at the beach in the summertime and a trip to Florida have given several long remissions.

The eruption has passed through several phases. First there was pruritus without eruption, then an eczematoid and exudative stage and finally the present phase, which presents discoid lesions on the back as well as on the aforementioned sites. For the past two years he has had a persistent plaque-like, raised, oozing erythematous eruption on the penis. Roentgenograms of the abdomen and the gastrointestinal tract showed a duodenal ulcer in 1941. Blood counts have been essentially normal. On one occasion there was an elevation of leukocytes to 19,250. A chemical examination of the blood showed urea nitrogen 8.2 mg per hundred cubic centimeters, creatinine 0.5 mg, uric acid 4.1 mg, sugar 123 mg and carbon dioxide-combining power 61.4.

#### DISCUSSION

DR JACK WOLF: I had occasion to see this man about two and a half years ago. He then gave a history of severe pruritus of one year's duration, he did not have a single lesion on the body at that time.

DR ISADORE ROSEN: I agree with the diagnosis of chronic exudative lichenoid and discoid dermatitis. The clinical features of the cutaneous manifestations resemble first a dermatitis venenata, and subsequently the lesions go through various stages of development, as described in the history. They may at any time resemble mycosis fungoides or one of the forms of lymphoblastoma.

DR HERMAN SHARLIT: Is there not a feeling that in some cases the disease is on a dermatitis venenata basis?

DR GEORGE C ANDREWS: I have the impression that in many such cases there is a generalized pruritus before the cutaneous lesions develop. Dr Costello says that the patient is of a high-strung, nervous disposition. I suspect that a neurosis is the underlying factor in many cases.

DR MAX SCHEER: Many of these patients are high-strung and nervous, which in all probability is a result of continuous and intolerable itching. In some cases the disease begins as dermatitis venenata or as a pityriasis-rosea-like eruption. I cannot get away from the feeling that some of these are cases of dermatitis venenata, and I strongly suspect that in a number of cases that I have observed the etiologic factor was the naphthalene used to keep moths away from the clothing. I saw 1 patient get well when his apartment was thoroughly cleared of naphthalene balls.

DR MAURICE J COSTELLO: This patient on one occasion went to Florida, exposed his body to sunlight and salt water and forgot his worries, and the eruption cleared. I agree with Dr Andrews that the patient is of a high-strung, neurotic type, having difficulty in the struggle for existence. All the patients I have seen suffering with this disease have been Jewish men of neurotic temperament between the ages of 35 and 40 years, most of them worked in the clothing industry, and they were improved by a change of climate or hospitalization. This man's eruption has passed through three stages: (1) pruritic, (2) eczematoid and exudative and (3) lichenoid and discoid. A biopsy performed by Dr Wilbert Sachs confirmed the diagnosis. The vessels throughout the middle and upper layers of the cutis were dilated, and about them was a pronounced cellular infiltration. The overlying epidermis was acanthotic, and at one point there was a Monro abscess. The cellular infiltration was composed of small round cells, numerous plasma cells and some epithelioid cells. A considerable amount of pigment was present. There was neither reticulum nor mitotic figures, nor were there any Pautrier abscesses or clumping of the nuclei.

### Disseminated Sarcoid with Pharyngeal Lesions Presented by DR FRED WISE

M C, a woman aged 39, referred by Dr Laird S Van Dyck, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Jan 12, 1943, with lesions of four years' duration. She was born in Puerto Rico, and has been in the United States for seventeen years. She has three children who are living and "well." The patient gives no history of previous cutaneous disease but had measles and chickenpox during childhood and pneumonia ten years ago. She feels dizzy and tired at times but is otherwise in fairly good health. She has been hoarse for the past year.

The eruption began four years ago as three pea-sized growths on the left cheek. A year ago similar lesions developed on the tip of the nose, upper lip and the root of the nose. Six months ago the other lesions appeared.

The lesions are located at the root and tip of the nose and on the right supraorbital region, both cheeks, upper lip, middle of the pinna of the right ear and lobule, right breast, arms and legs. They are almost symmetrically distributed and consist of irregular nodules from the size of a pea to that of a bean and larger, of slightly purplish hue and somewhat raised above the surface. They are soft, well defined, easily compressible and painful to touch. One large lesion involves the tip and the right ala nasi. The lesions on the left cheek have healed with some depressed scarring. The patient has a soft bean-sized growth on the left side of the pharyngeal wall. There are telangiectatic capillaries on the lesion of the nose.

The Wassermann reaction was negative, and urinalyses gave normal results. The hemogram showed a moderate anemia, a leukocyte count of 4,250, with 6 polymorphonuclear eosinophils, 7 monocytes and 14 (normal 3 to 5) band forms per hundred cells. Chemical examination of the whole blood gave normal values for urea nitrogen, nonprotein nitrogen, uric acid and dextrose. Examination of the blood serum showed total proteins, 7.6 mg per hundred cubic centimeters, albumin, 4.2 mg, globulin, 3.4 mg (normal 2 to 3 mg), ratio, 1.2:1 (normal 1.6 to 2.0:1). The ascorbic acid concentration in the blood plasma was 0.2 mg per hundred cubic centimeters (normal 0.7 to 1.4 mg). The sedimentation rate was 97 mg per hour by the

Westergren method (normal in female 15 mm per hour) Examination of the nasal smear was negative for lepra bacilli Intracutaneous tuberculin tests with concentration as low as 1:1,000 elicited negative reactions

A histologic section showed a sarcoid-like reaction The epidermis was thin and the rete pegs flattened The basal border was intact except in one area, where the basal cells were disorganized The entire cutis was occupied by an inflammatory reaction composed of epithelioid cells and a few round cells The cytoplasm of many of the epithelioid cells showed vacuolation Staining with carbolfuchsin did not reveal the presence of organisms

Roentgenograms of the hands showed multiple areas of rarefaction of various sizes surrounded by zones of condensation in the cortices of most of the phalanges Though as a result of the cystic-like changes in the cortices there was no expansion, here and there a slight subperiosteal outer cortical erosion was noted, being observed mainly in the middle phalanx of the middle finger of the right hand, with secondary soft tissue infiltration Moderate soft tissue swelling above some of the interphalangeal articulations was also noted The picture was considered to be such as is more frequently observed in sarcoidosis or granuloma other than tuberculous

Examination of the thorax showed little evidence of pathologic change A slight degree of hilar and root branch thickening, with interlobar accentuation, was observed on the right side This was thought to be probably puerile in origin, with no evidence of recent parenchymatous infiltration The heart was within the 10 per cent limit of normal

Ophthalmologic examination gave normal results Report of the neurologic examination on Oct 8, 1943 by Dr Stockfish follows "The neurologic picture was essentially normal except for a few signs The interosseous muscles and the thenar eminences showed slight atrophy There was some weakness in the opponens pollicis muscles It is my opinion that this condition is incidental to general malnutrition and rheumatoid arthritis in the hands I should say that there is no neurologic involvement"

Some of the lesions on the face were destroyed by electrodessication, but there has been recurrence

#### DISCUSSION

DR MAX SCHEER I accept the diagnosis of sarcoid, but had I seen the lesions only, without knowing the result of the tuberculin test or of the roentgenograms of the hands, I should have believed that the lesions, especially the one on the nose, were typical of lupus vulgaris

DR FREDERICK REISS (by invitation) I saw the slide of this case, and the histologic picture was not at all indicative of leprosy Referring to Dr Sachs's remarks, I think it is true that there is often confusion about vacuolation In the lepromatous type of leprosy, which is characterized by the richness of Hansen's bacilli, there are two kinds of vacuoles one a globus and the other a degeneration of the reticuloendothelial (foam) cells In such instances, if it were the lepromatous type of leprosy, one ought to find bacilli without difficulty If it were the sarcoid type of leprosy, one would expect such trophic disturbances as would be visible clinically and sensory disturbances to verify it Rarefaction of the bones does not exclude the sarcoid type of leprosy Dr Rabello, in Brazil, is almost convinced that what is called sarcoid is a mitigated form of Hansen's disease

DR FRED WISE The question of leprosy was of course taken up by the men who examined the patient, and the disease was excluded I think a degenerate process may be taking place in the muscles as in the bones, a cystic degeneration in the latter

**Acrodermatitis Continua** Presented by DR GEORGE M LEWIS

F C, a carpenter aged 58, removed a splinter from under the nail of his left ring finger eighteen months ago Shortly afterward there was swelling and pain in the region, followed by separation of the nail and subsequently by inflammation of the region of the nail bed Soon other fingers became considerably affected, the lesions being confined to the region of the nails In the course of treatment he received dressings which appeared to immobilize his hand A rash spread up the fingers and affected his hand and forearm This was later treated with wet dressings, with good response No lesions have ever appeared on his feet At present all the finger nails have been destroyed and all the nail beds are inflamed, showing redness, edema and some exudation The fingers show limitation of movement, apparently amounting to ankylosis of the second interphalangeal joints The fingers also show considerable atrophy, apparently from disuse Examination for fungi was unsuccessful

#### DISCUSSION

DR MAX SCHEER I thought the lesion with the undermined border on the left palm was typical of acrodermatitis continua or dermatitis repens of Crocker, which I believe are the same

DR FRED WISE The diagnosis as presented fits in with Hallopeau's disease, as far as one can tell now It is by no means a classic example, because the patient has lesions scattered elsewhere, which does not fit in with Hallopeau's acrodermatitis, implying dermatitis of the extremities

DR LLOYD H KEST (by invitation) I should like to suggest the possibility of arthropathic psoriasis Some of the lesions on the hand, especially on the thenar eminence of the right palm, look typical of psoriatic lesions The ankylosis present here would fit in with the diagnosis of arthropathic psoriasis

DR JACK WOLF In acrodermatitis of Hallopeau and in pustular psoriasis one expects to see pustules In the case presented tonight, I did not see any pustular lesions I wonder whether it falls into that category?

DR E WILLIAM ABRAMOWITZ What type of arthritis is involved, atrophic or hypertrophic?

DR FRED WISE It might be either or both

DR E WILLIAM ABRAMOWITZ This man never had arthritis at all, he has a disuse ankylosis From the appearance of the eruption of the nails and hand, it is the first real case of acrodermatitis that I have seen

DR GEORGE M LEWIS I think that it is correct to say that Hallopeau's disease typically involves one nail or one nail bed It seems to me that the history of injury in this case is important There was increasing involvement of the nails until all were affected, hence the disease was progressive rather than symmetric If Dr Abramowitz will come to Welfare Hospital, I will show him atrophic arthritis with psoriasis I think that the internists see more patients with atrophic arthritis and the dermatologists more with hypertrophic, because the latter are ambulatory

## CHICAGO DERMATOLOGICAL SOCIETY

MICHAEL H. EBERT, M.D., *President*MARCUS R. CARO, M.D., *Secretary*

Jan 19, 1944

## Pituitary Basophilism (Cushing's Syndrome)

Presented by DR. EDWARD A. OLIVER and (by invitation) DR. SAMUEL M. BLUEFARE

I S., a white woman aged 26, is presented through the courtesy of Dr. Arthur E. Mahle, of the Medical Department of Northwestern University. Her complaints on admission were amenorrhea of one and one-half years' duration, flushing of the face and dizzy spells.

About one year ago she was told that she had high blood pressure and diabetes. She had at that time polyuria, polydipsia and polyphagia, edema of the ankles and a tendency to bruise (ecchymoses) easily. An increase in weight became evident, from 150 to 250 pounds (68 to 113.5 Kg), and with this increase in weight the presence of striae became noticeable. At present her weight is 200 pounds (90.7 Kg).

At present the skin shows a lack of elasticity. Striae are noted on the anterior part of the shoulders, abdomen, thighs and back. Ecchymoses are present, and the skin in some areas is flabby. Perspiration is profuse in the axillae and on the palms. There has been an increase in the amount of hair on the face and body, although on the scalp the hair has become thin. The heart and lungs are essentially normal, and the blood pressure is 186 systolic and 130 diastolic. The patient presents all the features of Cushing's syndrome, namely, obesity, amenorrhea, weakness, high blood pressure, albuminuria, striae, ecchymoses and hypertrichosis of the face and trunk.

The urinalysis showed a 4 plus reaction for albumin but no sugar. The Kahn reaction was negative. The examination of the blood revealed 4,820,000 erythrocytes, 13,750 leukocytes with a normal differential distribution, and 15.2 Gm of hemoglobin.

The treatment to date has consisted of sixteen weekly roentgen ray treatments of 200 r each to the pituitary gland.

## DISCUSSION

DR. S. ROTHMAN (by invitation). A patient in the hospital with which I am associated displays the same fully developed picture of Cushing's syndrome as this patient does. But in addition to the striae she has loose atrophic spots on the elbows and knees, strikingly similar to lesions of acrodermatitis atrophicans. This combination makes me think of the possibility that the fragility of elastic fibers in acrodermatitis atrophicans is also of pituitary origin, acrodermatitis being overwhelmingly a disease of the menopausal age.

DR. MAURICE OPPENHEIM (by invitation). Concerning striae distensae (or atrophicae), which are so significant here, I want to direct attention to my investigations in cases of dermatitis atrophicans combined with striae. It is known that striae distensae are found in puberty, in adipositas and in severe generalized infectious diseases, for instance after typhoid. Striae are also found in pregnancy and after abortion at three months, but their absence is noted at times in spite of many pregnancies. One knows that dystrophic disturbances cause striae. My theory of the various types of striae distensae and of the various forms of dermatitis atrophicans is that they are on a congenital basis, due to a congenital or embryonal weakness of the elastic fibers, because in all these cases one finds

absence of elastic fibers or finds the fibers torn so that they cannot be stained. The resistance of the elastic fibers is decreased, in some rare cases because of glandular disturbances (puberty, pregnancy) and in other cases because of tension, where the border of elasticity is reached earlier than in normal skin (acrodermatitis atrophicans, extensor area of knee and elbow joints, striae adolescentium). The connective tissue, which must be separated from the elastic tissue does not suffer in the beginning, but later after the loss of the elastic fibers which form the skeleton of the connective tissue, it degenerates too.

DR. E. M. SMITH JR. I do not know whether the history mentioned this, but the patient has recently lost 50 pounds (22.7 Kg) in weight in a little while. The roentgenographic examination showed an abnormality of the pituitary gland.

DR. M. H. EBERT. I have been interested in the etiology of striae for some time. In 1934 I reported 2 cases of striae distensae of a peculiar hypertrophic type in young women with other evidences of endocrine disturbance (ARCH. DERMAT. & SYPH. 31:146 [Jan] 1935). While under observation the raised, bluish borders became transformed into pale atrophic striae of the usual type. I am of the opinion that in a case like this, of Cushing's syndrome, there is not simply a mechanical tearing of normal elastic tissue. I believe the elastic tissue has been injured by some toxic substance, which results in its fragmentation. In pregnancy and in certain types of endocrine imbalance observed in adolescent girls a similar process is involved.

## A Case for Diagnosis (Leukemia? Sarcoidosis?)

Presented by DR. CLARK W. FINNERUD and (by invitation) DR. CLARK F. JOHNSON

Mrs. R. G., a farmer's wife aged 37, was admitted to the Presbyterian Hospital on Jan. 15, 1944. Her complaints were "elbow trouble" since 1939, pain in the stomach since January 1944, diarrhea since Jan. 8, 1944, and temperatures of 100 to 101 F in the afternoons since Oct. 15, 1943.

In September 1935 the patient noticed that she had some small blisters on the inner side of her lower lip. She thought little of this, as she had had them periodically most of her life and they would just disappear. On this occasion the blisters broke and small ulcers formed on her lip, new blisters arose on the gums and tongue and these in turn broke down and small ulcerated areas resulted. This cycle kept up for some time. The patient went to the Central Free Dispensary in January 1936 for treatment of the sores in the mouth, and at this time she had four or five lesions on the breast resembling the lesions that she now has on her back. Biopsy was performed on these by Dr. Scull, and then they were treated with roentgen rays. They promptly disappeared.

She went to the Mayo Clinic in June 1937, seeking relief from the oral sores. A complete study was made there, and a lesion resembling those found on the breast was discovered on the left shoulder. This was elliptic, indurated, raised and reddish. Diet, gargles and various other medicaments, such as vitamins, had no effect on the oral lesions.

In October 1940 a small tumor was removed from the cervix of the uterus, and thereafter there was a constant flow until Nov. 20, 1940, when a hysterectomy and oophorectomy were performed by Dr. E. S. Denney at the Copley Hospital, Aurora, Ill. The patient was told that her ovaries and uterus were "diseased." She had no sores in the mouth after this operation.

and she attributes the cure to the surgical procedures. She states that a maternal aunt underwent a similar experience.

In November 1939 the patient felt a mass on the lateral aspect of her right elbow, approximately 1 cm in diameter. This was removed under local anesthesia, and she was told that it was a "fatty tumor." The healing was slow, and there developed a raised, hard mass that encircled the operative site, this was removed in January 1942, as it was causing considerable pain. There was another similar mass as big as a hen's egg on the medial aspect of the elbow. In September 1943 this mass was removed, and the incision has never healed completely. At this time she was told that there was a similar mass above the lateral aspect of the elbow about 10 cm above the original mass, but this has not been excised. In September 1943 she also noticed a hard indurated mass involving the medial side of the left eyebrow and upper lid and also a hard raised mass that can now be seen just below and lateral to the left eye. This has itched a great deal and at first increased in size but has become smaller in the last five weeks. Similar lesions, which are circular, raised, reddened and pruritic, have appeared periodically on the back of the chest, arms and legs. They vary in size and shape from day to day, getting larger and smaller at times, but they persist.

Some "small pimples" developed on the abdomen, chest, back, neck and arms on Dec 21, 1943. These also persist.

The glandular enlargement was noted first five years ago on the right side of the neck and this has progressed now to a generalized lymphadenopathy, but the enlarged glands on the left side of the neck were not noticed until Jan 2, 1944. These have become large, ache at the end of the day and pain more if they are scratched or rubbed. The large gland in the right inguinal region was first noted one week after the hysterectomy.

On examination of the skin there is a pinpoint-sized papular rash on the abdomen, chest, back, neck and arms. On the back, arms, legs and shoulders may be found the raised, indurated, coin-shaped, reddened areas from which a specimen for biopsy has been taken. Hyperkeratosis is noted on the surface of some of these lesions. To palpation they feel as if they penetrate deeply into the subcutaneous tissue. In the region of the right elbow and cubital space, scars can be seen where walnut-sized to egg-sized masses have been removed, as previously described. On the medial aspect of the elbow can be seen the poorly healed area, which is raised and indurated. There is a definite hypertrophy of the supraclavicular nodes on the left side. These are hard, multilobular and only slightly tender. They do not appear matted to the surrounding tissues or skin. The posterior auricular nodes on both sides are hypertrophied, and those in the anterior triangle of the neck on the right side are similarly hypertrophied. There is a single palpable node, of the size of a peanut, in each axilla, which is hard, movable and slightly tender. In the groins there is bilateral hypertrophy of the nodes, and deeper the smaller nodes can be felt.

On examination of the chest the excursions are greater on the right, with seemingly depressed activity on the entire left side of the chest. The pulmonary fields are clear to percussion and auscultation. The heart appears to be normal. There is pronounced tenderness with spasticity over the entire abdomen, especially over the upper left quadrant. There is a scar on the midline in the lower portion, with apparently good healing. The spleen is enlarged. The liver is

enlarged, dropping approximately 3 fingerbreadths on inspiration.

**Laboratory Data**—The examination of the blood showed 4,100,000 erythrocytes, 12 Gm of hemoglobin and 12,000 leukocytes, with 82 per cent eosinophils (adult cells), 11 per cent polymorphonuclears (adult cells), 6 per cent lymphocytes and 2 per cent mononuclears. The urine was normal except for a trace of albumin.

The agglutination titers of the blood were 1:20, 1:40, 1:80 and 1:120. There were no agglutinations with *Eberthella typhi* O, *Eberthella typhi* H, *Salmonella paratyphi* A, *Salmonella paratyphi* B, *Proteus* OX 19 and *Brucella abortus*.

Fluoroscopic examination of the chest showed nothing abnormal except for a healed Ghon lesion on the left in the fourth interspace, the colon was normal, the stomach was normal, but there was a mass in the epigastrium which was anterior and extrinsic to the stomach.

The temperature was 100 F on admission but has been normal since.

#### DISCUSSION

DR H. E. MICHFISON, Minneapolis. Since this patient has been so thoroughly studied and no definite diagnosis arrived at, the only suggestion that I can make is that the enlarged lymph nodes in the neck and the microscopic picture somewhat suggest Hodgkin's disease.

DR PAUL A. O'LEARY, Rochester, Minn. I saw this patient approximately five years ago, when she presented only one lesion on the shoulder and some lesions in the mouth. The examination of the tissue removed at that time was indeterminate. Today I favor a diagnosis of leukemia cutis, believing the exact type will be determined when a more typical blood picture eventually develops.

DR R. H. SCULL. I first saw this patient in 1937, in the department of allergy, at which time she complained of multiple recurring ulcers of the mouth and tongue. She later complained of some bluish red macular lesions of the right breast as a result of a child's pinching the breast while nursing. The slide presented today is a section of a biopsy specimen taken at that time. The physical and laboratory examinations, including blood tests and a blood count, showed nothing significant. I later saw her with two or more lesions of the same description on the back that came without the history of trauma.

DR LOUIS BRUNSTING, Rochester, Minn. The high percentage of eosinophils is of particular interest. It recalls a case in my experience, that of an elderly man who presented a chronic bullous eruption like erythema multiforme or dermatitis herpetiformis with pigmentation. The values for red and white blood cells were normal, but the percentage of eosinophils ranged well over 60 per cent. There were no immature forms, but within a period of less than a year the patient died, and shortly before death the white cell count total exceeded 200,000 per cubic millimeter. In the early stages these odd forms of lymphoblastoma are often not sufficiently differentiated to be identified.

DR UDO J. WILK, Ann Arbor, Mich. May I ask the presenters whether the enlargement of the lymph glands and the blood picture antedated the eruption?

DR C. W. FINNERUD. According to the history—and I have not all the points of the history clearly in mind, as I saw the patient for the first time night before last—the glandular enlargement preceded the appearance



of the cutaneous lesions. I saw the sections for the first time when they were brought over this afternoon. From the specimen that was taken yesterday afternoon from the shoulder it is evident that the disease is not sarcoid. When I saw her in consultation because of these plaques on the elbow, several on the back and over the left zygoma and the generalized lymphadenopathy plus the rather huge spleen and enlarged liver, I thought of the possibility of Schaumann's disease, but the chest and also the phalanges have been examined roentgenographically and there were no noteworthy changes there. I think eventually we shall find it is leukemia. As mentioned, the leukocyte count now is only 12,000. The differential count with 82 per cent eosinophils is particularly interesting. I could not see enough resemblance to Hodgkin's disease, at least in the sections, to warrant that diagnosis. Here again the eosinophil count is interesting. My feeling is that it will turn out to be leukemia.

**Pemphigus Vulgaris** Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS and DR M OTSUKA

Mrs A P, a Czech housewife aged 67, presents a generalized infiltrated inflammatory eruption of the skin on which are numerous variable-sized bullae, some of which contain clear fluid while others are lactescent, itching and burning sensations are present more or less constantly. The eruption has been present for about seven weeks, starting on the back about the scapular areas.

The Wassermann and Kahn reactions were negative. The urine was normal. Examination of the blood showed 60 per cent hemoglobin, 3,520,000 erythrocytes and 12,000 leukocytes.

The examination of a specimen removed at biopsy revealed the bullae to be unilocular and formed by the separation of the epidermis from the cutis. The blister contained fibrin and leukocytes, the majority of which were eosinophils. The papillae which formed the floor of the bullae were enlarged as a result of edema. The blood vessels in the deeper portion of the cutis were dilated and contained blood cells.

#### DISCUSSION

DR RUBEN NOMLAND, Iowa City. I am inclined to believe that this patient has pemphigus, but I am not absolutely certain. I wish, however, to make a report on some rather interesting features that have been noted in the last 5 or 6 cases of pemphigus that I have seen, that is, disturbances of the blood proteins. In 5 patients so far examined there has been almost always a decrease in the amount of protein in the blood, and almost always associated with this decrease there is an inversion of the albumin-globulin ratio, the globulin fraction being greater than the albumin. As nearly as I can tell from the limited number of patients studied, the greater the disturbance of the protein in pemphigus the more serious the prognosis. Unfortunately I have not had opportunity to check on other bullous disturbances to see whether they likewise are accompanied with disturbances of serum protein.

DR UDO J WILE, Ann Arbor, Mich. Probably all dermatologists feel that time is the thing that establishes the diagnosis of pemphigus in so many cases in which in the beginning it is difficult to make a differential diagnosis. This case, notwithstanding this woman's age, the extent of the eruption in seven weeks, the pronounced erythema and the configuration of some of the

lesions in annular form, impresses me more at the moment as one of a bullous erythema. I think that all dermatologists, however, have at times made the diagnosis of dermatitis herpetiformis and of erythema multiforme, only later to find pemphigus developing.

DR THEODORE CORNBLEET. I am inclined to agree with Dr Wile's diagnosis. The grouping of lesions, together with the excessive itching and erythema, points rather to erythema multiforme or dermatitis herpetiformis than to pemphigus. As is well known, the differential diagnosis among this bullous triad is often impossible early in the course of an eruption. There is a natural difference of opinion when such a picture is shown to a number of dermatologists. This emphasizes the need for an additional differential aid.

For this purpose I attempted to measure and compare the amounts of protein in the blister fluid and blood serum. It was found that the blisters of pemphigus, unlike those of some other bullous diseases, contained relatively more protein than blisters of erythema multiforme or of Duhring's disease. If there are many blisters present, it is inevitable that an appreciable amount of protein is withdrawn from the blood. The albumin molecule being much smaller, it escapes from the blood into the blister easily while the globulin is held back more readily. Consequently there is a tendency for a reversal of the normal albumin-globulin ratio in pemphigus. A similar situation is present in nephrosis. This altered ratio of the serum proteins, I believe, is merely a depletion phenomenon and carries no causal implications. Unfortunately, therefore, I believe it is useless to follow this lead in the hope of learning the cause of the disease.

DR FREDERICK R SCHMIDT. About fifteen years ago Dr William F Peterson and I studied these bullous eruptions. We found increased permeability in all bullous diseases, not only in pemphigus. We came to the conclusion that in addition to this there is also a constant alteration of the albumin-globulin ratio. But there was one factor that differentiated pemphigus from the other bullous diseases, and that was that the color index in pemphigus approached or exceeded 1. In the case of the woman seen this afternoon the earliest color index was exactly 1, in the second count it was over 1. I have noticed that in fatal and progressive cases the color index is constantly over 1.

DR M H EBERT. I think that every attempt to find some criteria whereby one can distinguish fatal pemphigus from the more or less benign bullous eruptions, dermatitis herpetiformis and bullous erythema multiforme, is valuable. From clinical observation I should say that this is a case of dermatitis herpetiformis. It has all the features. There is the eosinophilia both in the blood and in the bullous fluid, there are the characteristic itching, the edematous wheals, and the absence of lesions in the mouth. On the other hand, my clinical experience is that in cases of this type I am afraid the disease will eventuate fatally, so whether one calls it dermatitis herpetiformis or dermatitis multiforme or pemphigus makes little difference.

**A Case for Diagnosis (Heavy Metal Dermatitis?)** Presented by DR THEODORE CORNBLEET and (by invitation) DR H C SCHORR

R A, a Negro woman aged 32, has had an eruption since June 1943, which began on the forearms and about the waistline and was dry. It cleared during the application of an ointment. After this she was given twelve injections each in an arm and hip, though



the result of her blood test was said to be satisfactory. An eruption appeared which was scaly and not pruritic. It is not clear from the history that it followed immediately after an injection. Six more injections were given, and the patient said that these made the rash worse. Then the scaling gradually subsided, and it has remained in its present state for several months. It is the patient's opinion that the present conspicuous lesions resulted from the injections she received.

The less conspicuous changes in the skin on the extensor surfaces of the forearms and face appeared in October 1943, for which the patient was hospitalized for four weeks. The lesions were exudative and covered with crusts, and their character differed entirely from the earlier and drier ones. The moist eruption has greatly improved, to leave faint residues.

Now there are patches and plaques which coalesce to form sheets, especially over the upper part of the thorax. These are sharply outlined and scalloped in some places. There are lichenoid insets which show more scaling than the rest. All the lesions are fairly superficial. The pigmented areas have scattered through them other areas which are depigmented and sharply defined. On the extensor surfaces of the forearms and on the lower parts of the arms and on the face and neck is a faint erythematous dermatitis, slightly scaly and edematous in places and poorly outlined. The small amount of pigmentation at the latter sites contrasts with that present at the others. There is little itching. The gums and mucosae of the mouth have a normal appearance. There are moderately enlarged cervical lymph nodes, but the other accessible chains are not enlarged.

Sections of a biopsy specimen taken at a pigmented site were examined by the dark field method, but the appearance was not suggestive of a heavy metal as the etiologic factor.

Laboratory studies of the urine and blood while the patient was in the hospital recently showed nothing abnormal.

#### DISCUSSION

DR CLEVELAND WHITE. The appearance is suggestive of a possible contact dermatitis, but there is no history of her working with powder. I think the diagnosis as presented will turn out to be the correct one.

DR F W LYNCH, St Paul. The discrete nature of the papules, the hyperpigmentation and the distribution on the medial aspects of the thighs and flexor surfaces of the upper extremities point to a diagnosis of lichen planus. The microscopic picture is compatible with that diagnosis and does not show any particular evidence of toxic changes due to heavy metals. Since the patient is unable to give a satisfactory history as to the exposure to metals and the onset of the eruption, I prefer the diagnosis of lichen planus to that of a toxic eruption resembling that disease.

DR HERBERT RATTNER. I agree with Dr Lynch. Most of the lesions in this case strongly suggested lichen planus. Others simulated pityriasis rosea. They were all rather more deep seated than are lesions of these diseases usually, and they could well be manifestations of a drug eruption, perhaps of the biotrophic type.

DR MAURICE OPPENHEIM (by invitation). I agree with the diagnosis of Dr Lynch and Dr Rattner. I am not very familiar with diseases of the skin of Negroes, but if the same picture were present in a white person I would think of lichen planus atrophicus pigmentosus. The histologic picture does not speak against it. It may be influenced by the injections, which contributed to the pigmentations.

DR THEODORE CORNBLIET. There were many lichenoid lesions, but none that I felt were typical of lichen planus. The histologic changes, too, were in my opinion not confirmatory for this diagnosis. The history suggested that this was a lichenoid eruption following the administration of a heavy metal. Dark field examination of sections of tissue from the lesions, however, did not show any of the usual heavy metals to be present. I am uncertain whether this negative finding excludes the possibility that a heavy metal has caused these lesions.

#### Convex Finger Nails and Toe Nails with Nutritional Anemia. Presented by DR EDWARD A OLIVER and (by invitation) DR SAMUEL M BLUEFARB

M B, a white woman aged 22, presented herself for treatment of the peculiar formation of the nails of the fingers and toes. They present a convex surface, both longitudinally and transversely, the opposite of koilonychia and reminding one of club fingers. They differ from club fingers in that the pulps of the fingers are not distended and the phalanges taper normally. The nails are thicker than normal and have lost their luster. The nails of the thumbs and index fingers have been lost in the past, and the new nails coming in have assumed the formation of the previous nails.

At the age of 6 she had asthma and was found to be allergic to feathers, milk, rice and potatoes. At present she has no asthmatic symptoms. At the age of 11 she had lobar pneumonia.

The blood pressure was 108 systolic and 70 diastolic. The heart and lungs were essentially normal. The basal metabolic rate was +7 per cent. The urinalysis showed normal values. The Kahn reaction was negative. The hematologic examination showed 4,000,000 erythrocytes, 9,500 leukocytes with a normal differential distribution and 50 per cent hemoglobin.

#### DISCUSSION

DR ARTHUR C CURTIS, Ann Arbor, Mich. The type of nails presented by this patient was not the usual type seen in idiopathic microcytic anemia. Because the changes in the nails are of ten years' duration, they may be a manifestation of some type of congenital dystrophy.

DR S M BLUEFARB (by invitation). While it is true that in anemia one usually observes a spoon-shaped nail (koilonychia), there was a reference recently in *The Journal of the American Medical Association* to this type of nail with this type of anemia. A complete physical examination was made, and the only significant observations were the 50 per cent hemoglobin content and the low red blood cell count. It is our intention to give her liver and iron and to see what, if any, change can be observed in the nails.

#### Dermatitis Repens. Presented by DR E A OLIVER and (by invitation) DR H H RODIN

N H, a white woman aged 41, who resided on a farm in Tennessee until one month ago, was admitted to the dermatologic clinic, Northwestern University, on Jan 4, 1944. She complained of an eruption confined to the right thumb and right foot of nine months' duration.

The lesion began on the tip of the right thumb shortly after the part had been injured by a stem of a cotton plant and punctured by a needle, both events occurring on the same day and in the same area. One week later a similar lesion appeared on the lateral arch of the

right foot. She then had an attack of malaria followed by a more rapid spread of the existing eruption.

The past history contains nothing significant except that she had been treated for symptoms of menopause during the last year.

The examination reveals an acute inflammatory dermatosis confined to the right thumb and the lateral arch of the right foot containing numerous intraepidermal abscesses with undermining of the epidermis at the edges.

Treatment has consisted solely of local applications of 5 per cent sulfathiazole ointment.

#### DISCUSSION

DR UDO J. WILE, Ann Arbor, Mich. This did not look like dermatitis repens to me. It had a striking resemblance to a late syphilid. I wonder whether the patient has been investigated with regard to the presence of latent syphilis. The lesion on the sole had an atrophic scar and was entirely painless.

DR F. E. SENEAR. I had much the same feeling with regard to the possibility of dermatitis repens. It seemed to me that the central portion of the lesion on the foot, where healing had taken place, leaving a thin atrophic scar and no semblance of any activity such as is usually seen in dermatitis repens, would argue against that diagnosis. Also I felt that the lesion on the hand was made up of individual nodules in one part of the circumference. There were four or five individual nodules in one place.

DR M. H. EBERT. How long has the eruption been going on?

DR H. H. RODIN. Eight or nine months.

DR EDWARD A. OLIVER. The picture today is distinctly different from what it was when we saw the patient two weeks ago. There was considerably more infection present then. She was given a sulfathiazole ointment, and the eruption has improved greatly with that therapy. I, too, think that there is some question about this being dermatitis repens. The case should not have been presented with that diagnosis.

**Exfoliative Dermatitis (Psoriasis)** Presented by DR DAVID V. OMENS and (by invitation) DR M. OTSUKA and DR HAROLD D. OMENS.

B. A., a widowed Negress aged 52, a laundry worker, presents a generalized erythroderma, scarring of the medial aspect of the left leg and a bluish macular pigmentation of the deltoid areas and the bends of both arms.

The erythroderma has been present for the past four months. It started after the use of a white salve prescribed by the city health department, which burned and smarted on each application. The patient has had psoriasis for the past twenty-five years with the usual seasonal exacerbations and remissions.

She was treated for syphilis for ten years, with no treatment for the past four years. She also had been a morphine addict for twenty-two years, but she gave up the habit ten years ago. The results of a urinalysis and a hematologic examination were normal. The Kahn reaction was negative. Examination of the section removed at biopsy showed parakeratosis of the stratum corneum, absence of the stratum granulosum, uniform acanthosis with intercellular edema and spongiosis, slight clubbing of the papillary body, with dilatation of the blood vessels, and a perivascular infiltration of lymphocytes in the subpapillary portion of the corium.

#### DISCUSSION

DR HERBERT RATTNER. My information was that the exfoliative dermatitis had followed intravenous injections of some medicine. The exfoliative dermatitis cleared, and now there is visible the psoriasis.

DR JAMES H. MITCHELL. Psoriasis in a Negro is sufficiently rare to call itself to any one's attention. I talked to this woman today, and she recalled that I had taken a colored picture of her fifteen years ago. About two years ago I took another. I have here the original picture which showed a typical psoriasis on the knees and chin and no sign of exfoliative dermatitis at that time.

DR R. H. SCULL. I first saw this patient some years ago at Provident Hospital. The diagnosis of psoriasis was made and a photograph was taken at Rush Medical College. The lesions then were classic both in appearance and in distribution. I recall that when I brought her to the hospital for a biopsy some of the blue areas were typical of a morphine addict.

DR DAVID V. OMENS. This patient has had psoriasis for twenty-five years, she gives a history of having spent some time in jail. She has had no treatment for syphilis for the past four years, and she makes no mention of taking internal medicine of any kind. She was treated for psoriasis by the city board of health with applications of sulfur. She says that two or three times when she applied salve to the skin it became red with this generalized erythema.

**Psoriasis** Presented by DR DAVID V. OMENS and (by invitation) DR HAROLD D. OMENS.

J. S., an American married man, a bookkeeper, presents an eruption involving both hands, especially the fingers, on the palmar and dorsal surfaces. The eruption is composed of variable-sized papular lesions, definitely infiltrated, with a tendency to coalesce to form patches and covered with flaky scales. There is evidence of similar lesions on both elbows. On the hands there are fissures associated with the lesions which are painful and interfere with his occupation.

#### DISCUSSION

DR S. W. BECKER. In the absence of positive biopsy evidence I could hardly make a diagnosis of psoriasis. The lesion on the right elbow I thought was a little too low for a psoriatic lesion and was probably a neurodermatitis. The lesions on the palmar surface of the fingers resemble linear keratosis. The eruption is unique, but I do not believe that it is psoriasis.

DR MINNIE O. PERLSTEIN. To me this does not resemble clinical psoriasis. It resembles the lesions which we have been calling keratoderma climactericum. Men with this picture respond to endocrine therapy as do women. The picture this patient presents and the linear lesions on the tips of the fingers are usually seen at the onset. They progress and become a generalized keratoderma. The tips of the fingers become sensitive. I have a group of 4 women and 2 men whom I have been treating for the past three months with an ointment containing diethylstilbestrol. They are improving. In addition to the local therapy, I have been using testosterone propionate for the men and for the women diethylstilbestrol by mouth. When the endocrine therapy is discontinued, a relapse occurs which is controlled by resumption of endocrine treatment.

DR M. R. CARO. I agree with the diagnosis of psoriasis in this case. Several years ago we had

a patient at the University of Illinois with lesions on the knuckles which resembled the lesions here except that they were more shiny. A biopsy was performed and it showed the typical histologic picture of psoriasis. A few months later characteristic lesions of psoriasis developed on the elbow, further confirming the diagnosis. Since that time we have seen a considerable number of patients with identical lesions on the knuckles, for whom we made the diagnosis of psoriasis. It is my impression that when it is limited to this location psoriasis is generally mistaken for other dermatoses, especially neurodermatitis. Lesions of psoriasis on the knuckles are resistant to treatment.

**Kaposi's Sarcoma** Presented by DR HERBERT RATTNER and DR MAURICE DORNI

J C, a white man aged 74, presents an eruption on the feet and hands which first appeared about three months ago. There is a violaceous thickened patch covering each foot to the ankle in a "socklike" manner. There is a papule the size of a split pea on the left palm and a number of flat pea-sized papules on the ulnar side of the dorsal surface of each hand. There is no adenopathy.

Examination of the urine and blood gave essentially normal results. Histologic examination of a section taken from the foot showed the features of Kaposi's sarcoma.

DISCUSSION

DR NORMAN THOMAS, St. Louis (by invitation). The diagnosis appears to be Kaposi's sarcoma. I do not think that the lesions are benign, as the unusual configuration suggests invasion along the lymphatics.

DR MAURICE DORNI. We saw this patient several days ago, and we did not hesitate to make a clinical diagnosis of Kaposi's sarcoma. We were much impressed with the "socklike" distribution of the eruption and the rapidity with which it developed, if the history is correct, it is of only three months' duration.

**Blastomycosis** Presented by DR OLIVER S ORMSBY

W A L, a man aged 49, has had an eruption for five years. It began as a boil-like lesion on the right forearm. This spread peripherally, and new lesions developed in other situations. New lesions have developed recently on the lip and nose. At the present time there are lesions on the right forearm and elbow which present a thin cigaret-paper-like scar in the center while the upper and lower margins are crust covered and ulcerated. Similar lesions are present on the abdomen. There is a large fungating lesion on the lower lip and beside the nose. The patient has lost 40 pounds (18.1 Kg) in weight. The treatment in the past, both local and internal, has had little effect. The activity of the disease has been reduced about four fifths in six weeks' treatment. This consisted of four injections of arsphenamine and the internal use of potassium iodide together with a combination of vitamins.

DISCUSSION

DR E M SMITH JR. I have tried sulfadiazine in my 1 case of blastomycosis, and it seems to have better effect than potassium iodide. I have been trying to get some penicillin for use in a case of blastomycosis but have been unable to obtain any. There was a patient in one of the hospitals who was getting 500,000 units, so we have collected the urine, and an attempt will be made to extract it. About 85 per cent of the penicillin secreted in the first twenty-four hours can be recovered

DR OLIVER S ORMSBY. It seems rather superfluous to discuss blastomycosis at this time. I have heard from physicians all over the country who have treated blastomycosis with potassium iodide and also copper sulfate without much success. It was many years ago that I instituted treatment with arsphenamine. My colleagues and I would use potassium iodide until it ceased to be effective, when its use would be temporarily suspended. We would then give a series of three to five injections of arsphenamine, and then resume the administration of potassium iodide. In a comparatively short time good results were obtained. I am sure that this method of treatment is valuable and one that should be emphasized. The patient shown today illustrates this fact.

Within a few years Martin and Smith (Martin, D S, and Smith, D T. Blastomycosis [American Blastomycosis, Gilchrist's Disease]. I. A Review of the Literature, *Am Rev Tuberc* 39 275 [March] 1939, II. A Report on 13 New Cases, *ibid* 39 488 [April] 1939) concluded that patients resistant to potassium iodide are allergic. They proposed the use of a vaccine made from blastomycetes to reduce the hypersensitiveness and then use of potassium iodide. They got the same results by this method that we do with the arsphenamine and potassium iodide.

In the eight weeks we have been treating this patient, we used potassium iodide for one month and then gave four injections of arsphenamine and then returned to the use of potassium iodide. He has now had 80 per cent clearing, and I look for him to have entire clearing within a reasonably short time.

**Actinomycosis** Presented by DR E A OLIVER and (by invitation) DR ARTHUR GREENBERG

The patient, a Negro man aged 48 years, states that four months ago he struck his lower left side against the edge of a chair. The swelling appeared one week later and was rather painful. He states that the swelling has been lanced several times by his physician but that at times pus is discharged spontaneously. He has lost 19 pounds (8.6 Kg) since October 1943 but complains of no cough, night sweats or hemoptysis.

The examination discloses a palm-sized brownish area on the left side of the chest. There are several discharging sinuses in this indurated plaque. He also has a nodule on the back of the neck and a firm cystic mass on the lower third of the right thigh. This lesion is about the size of a small plum. Actinomycetes were found in the discharging sinuses in the lesion on the abdominal wall.

DISCUSSION

DR UDO J WILE, Ann Arbor, Mich. I think that there were some features of this case which did not fit in altogether with the usual case of actinomycosis. In the first place, actinomycosis usually involves bone. In the second place, two lesions in actinomycosis occurring at such widely separated points are also somewhat unusual. The fact that ray fungi may have been found in the discharge is of importance only if they are consistently found. It would have to be confirmed by more than a single examination. The patches he had on his thigh and foot are a great deal like cold abscesses. Tuberculosis of a rib or of the pleura could well go with the type of lesion he had in his chest. I think that before one accepts the clinical diagnosis of actinomycosis the case should be studied a little further, with regard to study for tuberculosis and also supplemented by a biopsy.

DR E A OLIVER The roentgenogram showed definite changes in the left side of the chest

DR PAUL A O'LEARY, Rochester, Minn Penicillin has been used successfully in the treatment of actinomycosis of both the cutaneous and the visceral types. The dose given approximates 500,000 Oxford units, and the less surgical intervention there has been the more satisfactory is the response

DR E A OLIVER I did not see the actinomycetes, but there is a good pathologist at the Veterans Hospital, who told me he has found actinomycetes on several occasions. I saw the patient thirteen days ago, and I thought that his disease was sufficiently interesting to bring him to this meeting. It has been a rather acutely developing case. The man has lived in Chicago all of his life. He worked for several years as a houseman. More recently he had been employed by the Campbell Soup Company. The lesions on the neck have just recently developed. The roentgenogram of the chest shows considerable infiltration in the left lung. The disease has developed so rapidly that I think one might well question the diagnosis. He has had some fever. I feel positive, however, that this is a definite case of actinomycosis

#### Multiple Hemangiomas Presented by DR E A OLIVER and (by invitation) DR ARTHUR GREFENBERG

The patient, a white man aged 52, states that he first noticed little wartlike lesions on the third finger of the right hand about four years ago. These lesions were diagnosed as warts and were cauterized. About six months later similar spots appeared on the right arm and in the region of the left elbow. These were also cauterized with acids. Shortly thereafter the lesions on the hands appeared. About two years ago the lesions on the soles of his feet appeared.

The symptoms are pruritus, worse at night, and bleeding when the lesions are slightly injured.

The Kahn reaction was negative. The blood count and urinalysis were normal. A biopsy from a lesion on the hand was made and was diagnosed by the pathologist at the Hines Veterans Administration Facility as multiple hemangiomas. There are thickened, reddish blue patches of irregular sizes and shapes on both palms, the plantar aspect of the feet, including the toes, and the lateral aspect of the right arm.

#### DISCUSSION

DR C W LANE, St Louis Unfortunately, I did not have a chance to see the section, and so my impression is purely a clinical one. The violaceous color of all the lesions, the warty excrescences on the surfaces of many of them and the history of their occurrences in areas of trauma, e g the biopsy site and burns, were indicative to me of Kaposi's sarcoma.

DR S W BECKER I should like to call attention to the fact that Kaposi's sarcoma per se is not a malignant tumor. It may become malignant later and eventuate in sarcoma, but ordinarily it should not be classed as a malignant tumor. Clinically I thought that this man presented Kaposi's sarcoma, but the sections showed a large number of endothelial cells around spaces filled with red blood cells. I believe that in consideration of the clinical picture a diagnosis of Kaposi's sarcoma could be made from the sections.

DR EDWARD A OLIVER I saw this man about three weeks ago and made a diagnosis of Kaposi's sarcoma. The histologic report was multiple hemangiomas. I could not correlate the clinical picture and the develop-

ment later in life with this diagnosis. To me it was Kaposi's sarcoma.

#### A Case for Diagnosis (Kaposi's Sarcoma?) Presented by DR E A OLIVER

A year and a half ago, while the patient was in the Army, an ulcer developed on the left leg shortly after he had struck it on the tail of an airplane. Later three other ulcers developed on this leg and have persisted without healing. In addition, he noticed a small ulcer on his scalp, it was excised and has healed. There has been only a slight loss in weight.

The examination reveals a fairly well developed, fairly well nourished white man of 23, not appearing acutely ill. The head and neck are normal except for a healed scar on the scalp. The heart and lungs reveal no abnormality. The liver, spleen and kidneys are not palpable. There are numerous large ulcerations on the left leg. On the left thigh there are several purplish subcutaneous nodules, firm in consistency. The ulcerations on the leg are rather deep, involving the muscles, covered with a necrotic material, and of ragged outline.

The roentgenograms of the chest revealed no abnormality. The cultures of the material from the ulcers revealed many gram-negative bacilli but no fungi. Examination of the biopsy specimen from the ulcers revealed multiple hemorrhagic sarcoma.

The blood count was within normal limits. The urinalysis revealed a faint trace of albumin. The Kahn reaction was negative.

#### DISCUSSION

DR H E MICHAELSON, Minneapolis I saw this patient after he had been in a military hospital for about a year. He had first been treated for pyoderma and ringworm, but later microscopic sections were diagnosed as Kaposi's sarcoma. Since there was such decided ulceration and the lesions clinically did not strike me as Kaposi's sarcoma, I had him go to Rochester, and Dr O'Leary was greatly surprised when the section that they made also suggested the diagnosis of hemorrhagic sarcoma. Since then the patient has had some metastases to the scalp, and I believe that his general condition has not changed much. Evidently the diagnosis is some form of sarcomatous malignant neoplasm, but it is hard to arrive at a final decision.

It must be remembered that "malignancy" is a clinical term, and, regardless of what the microscopic picture is, what the disease does to the patient is what determines how malignant the condition is.

DR PAUL A O'LEARY, Rochester, Minn As Dr Michaelson said, this case is unique. When I first saw this patient the possibility of a Kaposi sarcoma seemed remote, and as the histologic sections he brought with him, taken in two Army hospitals, were inconsistent with the clinical picture we performed another biopsy. Dr Montgomery favored a diagnosis of Kaposi's sarcoma, and the three general pathologists who examined the sections gave three different opinions, all tending, however, to favor a diagnosis of sarcoma of some sort.

Now that he has metastatic lesions of the scalp and from the numerous histopathologic studies that have been made, I favor a diagnosis of a hemangioendothelioma. An amputation was recommended some months ago but was refused by the patient, and now the process has gone too far for such a procedure.

DR S W BECKER I saw this section before I saw the patient. In view of the facts that spindle-shaped cells

extended deeply, more deeply than usual in Kaposi's sarcoma, and that there was an area of necrosis, which is not seen usually in Kaposi's sarcoma, I thought that the diagnosis should probably be spindle cell sarcoma. I think clinically also it is not Kaposi's sarcoma.

#### A Case for Diagnosis Presented (by invitation) by DR M OPPENHEIM

M S, a white man aged 27, presents an eruption on both shoulders partially on the neck, of red areas in ring form. These areas are 2 to 3 cm wide and are limited by single or confluent superficial blisters. The blisters have a whitish content and the rings of blisters are bordered by halos of inflammatory redness. The central areas are covered with normal skin. There are no pigmentations or scars. The lesion on the right side of the neck is the size of a walnut and is elevated, with indistinct borders and central blisters. The lesions begin with small superficial blisters surrounded by an intense red halo with indistinct limits, like impetigo simplex.

The disease started in 1934 with blisters and mild itching on the right shoulder. The patient was treated at that time with compresses of solution of boric acid and boric acid ointment. When I saw him a year ago, the diagnosis of impetigo serpiginosa was made and sulfathiazole internally and externally was used. After the internal treatment with sulfathiazole, the lesions cleared completely, but in a short time the eruption recurred. Sulfathiazole ointment had no effect. Later the patient was treated with injections of oidiomycin, acetarsone and grenz rays without favorable results.

The Kahn reaction was negative. The urinalysis and blood count were normal. The smear of the blister fluid revealed intracellular and extracellular staphylococci.

#### DISCUSSION

DR NORMAN TOBIAS, St Louis: I had the impression that this was a case of Hailey and Hailey's type of benign pemphigus, based on the duration of ten years, the absence of constitutional symptoms, the frequent remissions and exacerbations, the localized nature of the patches, composed of crusted and bullous elements, and the resistance to treatment. Although there was no history of other cases in the family I have seen 2 or 3 cases in which there was no hereditary history.

DR M H EBERT: I am glad to hear Dr Tobias make this statement. That was my clinical diagnosis.

DR F W LYNCH, St Paul: A few years ago I presented a patient with a similar eruption at a meeting of the Minnesota Dermatological Society. I regarded that case as one of the benign dyskeratotic bullous eruptions described by Hailey and Hailey as benign pemphigus. I believe that Dr Oppenheim's patient has the same disease, even though the history of familial involvement is absent. In my patient, as in Dr Oppenheim's, the eruption responded temporarily to the oral administration of sulfathiazole.

DR S W BECKER: I think that is what Dr Obermayer and I called dyskeratosis bullosa hereditaria. The human generations are so far apart that one neglects to find out whether a man's children acquire the disease. It usually comes on at 18 years of age. We have seen 2 or 3 instances in which there was only one member of a family involved, but it may be that their cases may be the beginning of the disease on a familial basis.

DR THEODORE CORNBLEET: Because of the dyskeratosis that is present may I suggest that Dr Oppenheim determine the vitamin A level of the blood and also perhaps administer this vitamin therapeutically?

DR MICHAEL H EBERT: What would be the basis?

DR THEODORE CORNBLEET: The basis for this suggestion is the similarity of the fundamental histologic change, namely, dyskeratosis both in this patient's lesions and in keratosis follicularis. The similarity is so great that some investigators believe that benign familial pemphigus is a variant of Darier's disease. If the same therapy should be equally successful in the two diseases, this would not prove their identity. Thus a lack of dietary vitamin A may produce a keratosis of the follicles, and the same factor has been successfully employed in treatment of Devergie's disease. Both show the common denominator of keratosis of follicles and improvement from the use of vitamin A and yet are not identical.

DR MAURICE OPPENHEIM (by invitation): I do not think that this is a case of familial pemphigus. It is also not epidermolysis bullosa hereditaria. The disease started eleven years ago, and the patient was treated in New York at the Skin and Cancer Hospital, with no favorable effect. I have watched the case since December 1943 and thought first of impetigo circinata serpiginosa, because the cutaneous lesions started always with a superficial impetiginous pustule, healing without a scar. In the smear staphylococci were present almost in pure culture, the intracellular and extracellular effects of the therapy with sulfathiazole internally led me to believe that it was a case of impetigo serpiginosa recidivans. Impetigo herpetiformis in women with puerperal sepsis, in pregnant women and, in some rare cases, also in men remind me very much of this eruption. I believe that one sees here a chronic superficial infection with some kind of staphylococcus which is extremely resistant. One may call this eruption "pyodermatitis superficialis serpiginosa."

DR M R CARO: Was a biopsy performed?

DR MAURICE OPPENHEIM: No.

DR M R CARO: May I suggest that a biopsy be performed before anything further is done?

DR THEODORE CORNBLEET: This man showed a typical Nikolsky sign, which occurs in familial pemphigus.

DR MAURICE OPPENHEIM: I was never able to produce a Nikolsky sign. I do not think this eruption belongs to the pemphigus group, because it is too localized, just on the shoulders. After eleven years of duration dermatitis herpetiformis or another type of pemphigus vulgaris would show lesions in other parts of the body. The mouth is free, and the whole body except the shoulder areas is free. The lesions have always been localized in the same place.

#### Ocular Pemphigus Presented by DR E A OLIVER and (by invitation) DR B H WEINSTEIN

The patient, a Negro aged 46, states that in December 1942 a blister appeared on the right buccal mucosa which disappeared spontaneously in one week. He had a sore throat in February 1943. In April 1943 he had a recurrence of his sore throat and some epiphora of the right eye. The Wassermann reaction was reported negative in April 1943, but his symptoms gradually became worse, involving the mouth and throat as well as both eyes. He also complained of hoarseness at that time. In October 1943 he noticed a vesicle on his left leg, and this left an erythematous, slightly granulomatous patch. In November he noticed similar lesions on his right leg and on the scrotum. There has been a 20 pound (9.1 Kg.) loss of weight in ten months.

The Kahn reaction was negative. The urinalysis was normal, and the Frei test was slightly positive. The



hematologic examination showed 60 per cent hemoglobin, 2,970,000 erythrocytes and 3,600 leukocytes with 55 per cent polymorphonuclears, 37 per cent lymphocytes, 6 per cent eosinophils and 2 per cent basophils.

The examination shows a medium-sized Negro with decided thickening of the conjunctiva, which is spreading across the cornea in both eyes. The palpebral fissures are narrowed, and there are considerable synechiae. The larynx, buccal mucosa, pharyngeal-lingual mucosa, palate, front of the mouth and laryngeal mucosa are covered with a whitish deposit superimposed on a reddish base. On the scrotum and legs are the evidence of old bullae. The examination of the rectal mucosa shows superficial mucosal ulcerations measuring 0.5 by 1 cm.

#### DISCUSSION

DR OLIVER S. ORMSBY: For at least thirty or more years I have stood up before this society and stated that there was no such thing as pemphigus of the eye. I was always convinced that patients had a sclerosing disease of the eye, but I thought that it was different from the pemphigus that occurred on the skin. In the last eight years, since Klauder and others (Klauder, J. V. *Essential Shriveling of the Conjunctiva [Ocular Pemphigus]*, *Pemphigus of the Mucous Membranes*, *ARCH. DERMAT. & SYPH.* 38:988 [Dec.] 1939; Klauder, J. V., and Cowan, A., *Ocular Pemphigus and Its Relation to Pemphigus of the Skin and the Mucous Membranes*, *Am. J. Ophth.* 25:643 [June] 1942) have made convincing contributions on the subject I have changed my mind and now believe there is an ocular pemphigus. The majority of these patients have few bullae on the skin, they have most of the lesions on the tissues of the eye, and on other mucous membranes, mouth, throat and vagina. After a few years the conjunctiva becomes atrophic and sclerotic. Vision is greatly impaired or destroyed. This condition is developing in this patient. I think that this is an example of ocular pemphigus with bullae on the skin, and I think the patient's chances of getting it cleared are very limited. In the majority of cases it has been extremely resistant to treatment.

DR LOUIS BRUNSTING, Rochester, Minn.: In early pemphigus there is no depletion of the protein in the blood and no alteration of the albumin-globulin ratio or of the electrolytes. Only in the late stages, when much of the skin has been denuded and there has been a sizable transudation of fluid, do these changes occur.

DR EDWARD A. OLIVER: I have not much to add except to say that I feel that this is a classic example of ocular pemphigus. In addition to bullae in the inguinal region, on the leg and on the mucous membranes, proctoscopic examination reveals similar lesions in the lower part of the bowel.

Therapy was begun twelve days ago. It consists of acetarsone 0.25 Gm. three times weekly, the dose being gradually increased, and large doses of vitamin D. He has improved considerably in the last two weeks.

#### Angiokeratoma Corporis Diffusum (Mibelli) Presented by DR SAMUEL J. ZAKON

M. K., a man aged 49, born in Poland, states that he first noted the appearance of lesions about twenty-five years ago. They appear as pinhead dark brown to black spots and grow at a very slow rate. In the course of years they grow to the size of a nodule. He had suffered from varicose veins and disturbance of the peripheral vascular circulation. He received injections of sclerosing solutions in the veins and noted a decided improvement of the varicosities. A few years ago one large lesion was excised by a surgeon, and the histologic

report was hemangioma. A number of the smaller lesions on the face were electrodesiccated. Some recurred. His parents and the other members of his family are still in Europe, hence he cannot state whether other members of his family suffer from a similar disease.

The examination reveals the presence of numerous discrete lesions situated on the face, arms, chest, thighs and legs. They are dark brown to dark purple and vary in size from that of a pinhead to that of a small nodule. The older lesions are elevated and have a distinctly warty appearance. The size of the lesions apparently depends on the age.

A lesion of the thigh was removed for histologic study, and the sections show blood-filled subepidermal and intraepidermal lacunas, hypertrophy of the stratum corneum and hypertrophy of the rete.

#### DISCUSSION

DR UDO J. WILE, Ann Arbor, Mich.: I am extremely interested in this case. The angiokeratoma of Mibelli has up to within recent years been incorrectly described in the textbooks of dermatology as small angiomatous lesions of the scrotal sac. These have nothing whatever to do with the angiokeratoma of Mibelli, which is usually found on the extremities and is commonly due to vascular injury, particularly following frostbite. The lesions are typical. They present themselves as angiomatous lesions with atrophy and always associated with hyperkeratotic lesions.

The disease is actually a rare one, at least in this part of the country, and I believe that this is the third case that I have seen in which the diagnosis of angiokeratoma is clearcut.

DR H. E. MICHELSON, Minneapolis: We have recently had a patient with this rare disease, and after reviewing the literature I agree with Dr. Wile that there are many cases reported in which the diagnosis is not justified. We came to the conclusion that our patient's disease was based on vascular changes, and it is my opinion that angiokeratoma should be classified as a vascular disease.

DR S. J. ZAKON: There is a picture in Jadassohn's "Handbuch" (Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1932, vol. 12, pt. 2, p. 425) that illustrates the same type of angiokeratoma as this patient presents. The pictures in the American textbooks usually show the hands, fingers and face. This picture in Jadassohn's "Handbuch" shows the legs and trunk. The histologic section which I showed is characteristic. The young woman who makes our sections looked at the slide, opened up Kyrle's histopathology (Kyrle, J. *Vorlesungen über Histo-Biologie der menschlichen Haut und ihrer Erkrankungen*, Berlin, Julius Springer, 1925, vol. 1, p. 265) and made the diagnosis before any one else, because this section is an exact duplicate of the colored picture in Kyrle's book.

#### Blastomycosis with Furunculoid Lesions Presented by DR F. E. SENEAR and DR M. R. CARO

A. T., a man aged 26, had pleurisy in March 1943. While he was in the hospital several small lesions developed on the left ankle. About May 1 he noticed that the left ankle had become swollen and tender. The pain increased so that weight bearing became impossible. About this time pea-sized papules appeared on both thighs and on the left buttock. These lesions gradually increased in size and became crusted.

On July 26 the patient was seen at the University of Illinois Dispensary for the first time. The left ankle



was in a cast. On each thigh and on the left buttock were quarter to half-dollar sized, crusted, violaceous plaques. On the tip of the nose there was a walnut-sized, crusted, cauliflower-like lesion with numerous tiny pustules in the periphery. The lesion had been present about four weeks.

The examination of the left ankle after the cast was removed revealed a crusted ulcer of BB shot size and a small fluctuating abscess with blueness of the overlying skin. Blastomycetes were found in pus from the lesion on the nose and in pus aspirated from the abscess on the ankle.

The microscopic examination of a biopsy specimen from the left ankle showed blastomycosis. The roentgenogram of the left ankle showed irregular areas of decalcification probably due to secondary atrophy. Roentgenographic examination of the chest showed nothing significant.

The patient has been treated with potassium iodide since the diagnosis was established. All the lesions have improved greatly. There is little discharge from the lesion on the ankle at present, and the patient is able to walk without crutches.

#### DISCUSSION

DR F E SENEAR. I want to add a word about the patient. We saw him for the first time some months ago in another service in the hospital. At that time he had two plaques of blastomycosis on the thigh. One of the residents recovered blastomycetes. We were unable to find out what was done in the way of treatment, but those two lesions healed. He came back to us with a cast on the ankle. He had been seen in the orthopedic department, where it was thought he had a scrofulodermatous lesion on the ankle. He had at that time a typical lesion of blastomycosis on the nose, which responded well to potassium iodide. While receiving potassium iodide for this the ankle improved rapidly. When the cast was removed, we found that he had a series of four small abscesses on the ankle not resembling at all the ordinary vegetative form of blastomycosis. We were able to get a small amount of pus from one of the abscesses which was fluctuating. Blastomycetes were present in great profusion in this pus, there being about 20 or 30 to the field. I think that I have never seen a specimen in which it was easier to find the organisms.

We have seen but few cases of the furunculoid type of lesion. I had 1 other patient with a typical blastomycosis of the hand who had a lesion of cold abscess type on the flexor surface of the forearm. It was easy to recover the organisms from this abscess also. Roentgen studies of the ankle showed nothing except some rarefaction which was thought to be due to disuse of the extremity while the patient was using crutches. We have not been able to determine any systemic involvement as yet.

DR MINNIE PERLSTEIN. The first symptom this patient had was pleurisy with effusion in which tubercle bacilli were not found.

DR F E SENEAR. That pointed to the possibility of its being a tuberculous disease of the ankle.

DR M H EBERT. Are these lesions similar to those seen in systemic blastomycosis?

DR F E SENEAR. They are similar, and they respond to treatment. As soon as this man received treatment for the lesion on the knees, the ankles began to improve symptomatically, so that in three months he was walking without crutches and just wearing a cast. When we found so many blastomycetes we started use of potassium iodide and the lesions healed.

Morphea Presented by DR J H MITCHELL and (by invitation) DR FRANCIS W HETREED

S S, a woman aged 38, of Polish descent, first noticed changes in the skin in the lower abdominal region four and one-half months ago, which was six weeks after the delivery of her last child.

She first noticed a dollar-sized patch in the region of the right lower quadrant of the abdomen. In rather rapid succession other areas under the breast and on the sides of the abdomen developed. The most recent lesion is over the upper surface of the left scapula. Itching has been present since the onset.

On examination, there are noticed various lesions from the size of a quarter to that of a palm and hard to the touch. The initial lesion in the right lower quadrant of the abdomen has assumed a brownish color with striae gravidarum evident within the patch. Other lesions show the brownish center with the middle area normal in color, this in turn surrounded by a violaceous halo.

The skin of the head, neck and extremities is normal.

The Wassermann and Kahn reactions were negative. There were 3,900,000 erythrocytes and 6,000 leukocytes. The phosphorus level of the blood was 39 mg per hundred cubic centimeters.

#### A Case for Diagnosis (*Erythema Multiforme*?)

Presented by DR THEODORE CORNBLEET and (by invitation) DR DAVID COHEN and DR H C SCHORR

M F, a white woman aged 30, has had an eruption on the arms and forearms for four weeks.

The lesions are grouped vesicles which dry to form scaling, erythematous, nonatrophic areas. New vesicles form about the sites, they are somewhat umbilicated and are about the size of the head of a match. New lesions continue to form after four weeks.

Three months ago the patient was hospitalized for a rectal complaint, and hemorrhoids were removed. Shortly afterward she began to have a septic type of fever. At about this time lesions developed over the tibias, which were diagnosed as erythema nodosum. These have since undergone involution. There were malaise and night sweats and then the present eruption appeared on the arms. There was a systolic murmur at the mitral area which was detected for the first time simultaneously with this last rash. The internists entertained the diagnosis of rheumatic fever. The patient has been rather uncooperative and refused to allow a biopsy to be made.

The examination of the urine gave normal results. The examination of the blood showed 4,630,000 erythrocytes, 12,000 leukocytes and 69.6 per cent hemoglobin. The differential distribution showed 53 per cent segmented forms, 36 per cent small lymphocytes, 8 per cent monocytes and 3 per cent stab cells. Culture and examination of fluid blister showed nothing noteworthy.

The stool contained blood, and *Shigella alkalescens* was cultured from it.

The tuberculin patch test elicited a positive reaction. The roentgenographic examination showed calcification in the right lung and paratracheal glands.

Treatment included the use of sulfadiazine, ascorbic acid and vitamin B complex.

#### DISCUSSION

DR C W LANE, St. Louis. This patient is extremely hypochondriac, and in the case of such persons dermatitis factitia must always be considered, but the present eruption is not of a bizarre type and is present

in relatively inaccessible regions. The patient stated rather boastfully that since an operation three months ago, she has been taking nine different kinds of pills and three different kinds of liquid medicine daily. With this history and the presence of a diffuse papular, vesicular, bullous, erythematous eruption, it is my opinion that this is a drug eruption, most probably due to bromides.

DR M H EBERT: I am inclined to agree with Dr Lane that this is a bromoderma. I presume it could be classified under symptomatic erythema multiforme.

DR THEODORE CORNBLEET: We were unable to make a definite diagnosis and used a questionable erythema multiforme as a focal point for discussion. I agree that drugs may be the cause of this eruption. The patient took bromides but not recently. A bromide eruption, however, as is well known, may continue long after the drug has been taken. Since we know that the patient did take bromides the finding of them in the urine or blood does not prove the etiologic relation to the eruption. A therapeutic test with sodium chloride may be more helpful in determining this point.

**A Case for Diagnosis (Pityriasis Rubra of Hebra?)** Presented by DR THEODORE CORNBLEET and (by invitation) DR DAVID COHEN and DR H C SCHORR

M T, a white woman aged 70, has had an eruption for eight years which began on the thighs and spread gradually to become almost universal. It consists of an erythroderma with fine branny scaling. There is little itching. On the back are what appear to be normal areas of skin as small island insets. There is a diffuse atrophy of the forehead, cheeks, forearms and legs. There is slight involvement of the palms and more of the soles. The toe nails are hyperkeratotic and raised above their beds by debris. The finger nails are striated. The lips and tongue are atrophic, with the latter displaying a purplish cast.

The hematologic studies, which included serum tests for syphilis, cells counts, differential counts and chemical examinations, all gave normal results. There was nothing abnormal about the urine. Tests indicated that hepatic function was satisfactory. The vitamin A concentration was 14 micrograms per hundred cubic centimeters of blood and the carotene concentration 55 micrograms. Roentgenographic examination of the chest showed nothing abnormal.

Histologic examination showed a thin scale with islands of parakeratosis and an epidermis which in parts was flattened. The granular layer was discontinuous, there was a slight intercellular edema throughout the epidermis, and the basal layer was intact, although it showed ballooning of many cells. In the upper part of the corium there was a well defined horizontal band in which lay many densely packed foci composed of dilated and engorged blood vessels surrounded by lymphocytes, lymphoblasts, histiocytes and chromatophores filled with granules of melanin. The elastic fibers were thinned and fragmented in the zones of the infiltrate but were not entirely destroyed.

#### DISCUSSION

DR HERBERT RATTNER: It was my impression that this patient had a scaly erythroderma on a senile skin. Perhaps later it will be possible to establish other evidence of lymphoblastoma.

DR MAURICE OPPENHEIM (by invitation): It may be dermatitis herpetiformis superimposed on dermatitis atrophicans. The histologic features indicate dermatitis atrophicans.

DR F W LYNCH, St Paul: I agree with Dr Rattner's impression as to the presence of atrophy. The eruption has some resemblance to the poikiloderma-like changes described by Lane and others in association with certain instances of lymphoblastoma. A somewhat similar case was described by Hazel in 1939 (Hazel, O G. Poikiloderma Atrophicans Vasculare. Report of a Case with a Review of the Recent Literature, ARCH DERMAT & SYPH 40 276 [Nov] 1939).

DR THEODORE CORNBLEET: We thought of pityriasis rubra of Hebra, but there are several arguments against that diagnosis. Atrophy is an integral part of Hebra's entity but is lacking over the greater part of the present eruption. Pigmentation, too, is a feature necessary for such a diagnosis but is not present here. Pityriasis rubra of Hebra has been shown latterly to eventuate into a frank lymphoblastoma rather than the tuberculosis previously observed by writers. We naturally are watching for a leukemic or related outcome. In the meantime we favor another possibility. It was undoubtedly noticed that this patient had a low level of vitamin A in her blood, namely 14 micrograms per hundred cubic centimeters. This is definitely in the pathologic range. The erythroderma, ectropion and other changes are not unlike what may be expected in pityriasis rubra pilaris. Others as well as we have found low vitamin A values in the latter disease hence the values found in this case are confirmatory of such a diagnosis. This woman showed something else in support of this, that is, the few normal islands of skin within the sea of erythroderma.

**Xanthomatosis with Tendon Xanthomas** Presented (by invitation) by DR S ROTHMAN and DR A B HENNINGSEN

The patient, a 28 year old white woman, was admitted to the department of surgery of Albert Meiritt Billings Hospital on Oct 27, 1943, with signs similar to those now present. The first lesion appeared six years ago on the dorsum of the right hand. The other lesions have gradually developed in the last three years. The tendon lesions have all been growing during the past year. There have been muscle pain, migrating joint pain and stiffness for one year.

Gastrointestinal symptoms consisting of belching, nausea, pain of the abdomen in the right upper quadrant and distention of one year's duration pointed to the possibility of gastrointestinal involvement and cholesterol stone formation in the biliary system. A cholecystogram, however, was normal.

The patient's mother had similar lesions on the eyelids, over the knuckles and on the achilles tendons. No other relatives are known to have been affected.

There are firm hard nodules covered by normal skin over the right olecranon process, also tumors obviously attached to the extensor tendon sheaths over the second and third metacarpophalangeal joints of both hands and multiple nodules in the patellar and achilles tendons bilaterally, over which the skin is movable. A cutaneous xanthoma is present adjacent to the medial canthus of the left eye.

The laboratory examination revealed the following values for lipids in the blood:

Date	Total Lipids, Mg /100 Cc	Total Cholesterol, Mg /100 Cc	Free Cholesterol, Mg /100 Cc
10/28/43	1,577	430	320
11/22/43	1,602	430	258
12/23/43	1,620		
1/7/44		210	151.3
1/17/44		231	152.7

Other laboratory examinations, including blood counts, urinalysis, determination of the Kahn reaction and roentgenographic examination of the chest, skull and bones of the right hand and right ankle, revealed no abnormalities.

The condition of the patient was not essentially influenced by a low cholesterol diet. The recent improvement of the blood cholesterol level may be due to the administration of lipocain (26 capsules per day for several weeks and 18 capsules more recently) over a period of three months.

Histologic examination showed typical xanthoma structure.

#### DISCUSSION

DR ARTHUR C CURTIS, Ann Arbor, Mich. This case was interesting to me because it emphasized one thing that Dr Hamilton Montgomery has emphasized, the frequent incidence of cardiovascular disease in a patient with xanthomatosis. This patient's mother died at 52 of coronary occlusion. She said that her mother's family was "filled with cardiovascular disease." In addition to the xanthomas of the tendons she had a xanthelasma on the eyelid. We have made studies of the blood fat of 39 patients who have xanthoma palpebrarum. Eight receiving 15 Gm of lecithin daily were followed for from forty-six to one-hundred and eighty-nine days. Unfortunately these patients have had no changes in the xanthelasma lesions or any fall in blood fat levels.

DR S ROTHMAN (by invitation). The blood lipid values have come closer to normal since the patient has been given lipocain, a pancreatic substance which was isolated by Dr L R Dragstedt at the University of Chicago.

#### Disseminated Lupus Erythematosus Presented by

DR J H MITCHELL, DR R H SCULL and (by invitation) DR FRANCIS W HETREED

J B, a woman aged 48, of Irish descent, first had an eruption on her nose twenty-five years ago. It spread gradually to involve both cheeks and the chin. Three years ago the lesions appeared on the hands and arms, but they subsequently disappeared. They recurred on the hands three months ago and now are spreading up both arms. The lesions about the mouth and chin healed with atrophy.

Her husband is living, as well as two children, 25 and 18 years old. There were two miscarriages, about seventeen years ago.

Examination shows practically complete involvement of the nose, both cheeks and chin. The lesions are erythematous, scaling, keratotic and grouped. On diascopic pressure a few small brownish nodules are seen. The extensor surface of both arms and forearms show erythematous slightly scaling lesions. The dorsal surface of hands and fingers show lesions with a relative freedom of the middle phalanges, especially on the right side.

The temperature was normal. Examination of the blood showed 4,500,000 erythrocytes and 8,200 leukocytes. The Wassermann and Kahn reactions were negative. The differential count showed 65 per cent neutrophils, 30 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils.

#### DISCUSSION

DR ARTHUR C CURTIS, Ann Arbor, Mich. I agree with the diagnosis of lupus erythematosus. I think it

interesting, in view of some of the recent work that has been done in a similar disease, that is, periarteritis nodosa, that many features of lupus erythematosus and periarteritis nodosa are the same. There has recently been reported, in the *Archives of Pathology*, a case of lupus erythematosus in which the clinical history pointed to an allergic cause for the disease. We have recently studied a patient in the University Hospital by determination of the leukopenic index after exposure to ultra-violet irradiation. The leukocytes fell from 6,500 to 3,000 and then, with the development of the erythema, went to 9,500 and then fell to the normal level in a twenty-four hour period. This type of reaction suggests a definite allergic reaction, in this case to light.

DR H E MICHELSON, Minneapolis. I cannot let this case go by without asking either Dr O'Leary or Dr Brunsting to tell us on what symptoms they base their prognosis in cases of acute lupus erythematosus. When these patients complain of great fatigue, it means considerable to me.

DR PAUL A O'LEARY, Rochester, Minn. The diagnosis of chronic disseminated lupus erythematosus seems warranted in this case. For several patients we recently made the diagnosis of disseminated lupus erythematosus before they manifested the cutaneous signs of the disease. In young women who complain of pains in joints without roentgen evidence of bony changes, a mild degree of fever, a high sedimentation rate and a leukopenia, a diagnosis of acute or subacute disseminated lupus erythematosus is usually warranted, even though there are no lesions present.

DR LOUIS BRUNSTING, Rochester, Minn. I should like to emphasize some points in dealing with the early phases of disseminated lupus erythematosus and also the differentiation of the disease from dermatomyositis. It is well known that young women are particularly affected and that for a number of months before onset of the eruption there may be vague complaints such as malaise, fatigue and, particularly, transient arthralgias. The laboratory analyses often show secondary anemia, leukopenia, an increased sedimentation rate of the erythrocytes and sometimes albuminuria. In such patients, under provocation of sunlight, infection or some other mechanism, the cutaneous signs may first appear. The reaction of the patient seems to be out of proportion to the insult, as though the person had been sensitized by some previous episode, and in the history of these cases I believe emphasis should be laid on the search for past infections, particularly those of the streptococcal group, such as rheumatic fever and chorea. There are similarities among the syndromes of disseminated lupus erythematosus, subacute bacterial endocarditis and periarteritis nodosa.

In dermatomyositis the patient may be an adult or a child and the first complaints have to do with tenderness and stiffness of the muscles rather than the joints. There may be edema of the face and extremities and a suffusion of the skin over the face and neck of a violaceous hue, the so-called heliotrope eyelids are distinctive. There may be violaceous scaling plaques over the knuckles, elbows and knees as the earliest signs of the eruption. Usually there is no leukopenia or elevation of the sedimentation rate unless there is fever, but a consistent abnormality is noted in the form of creatinuria, which waxes and wanes in the various stages of the disease. This seems to be an end result of the degenerative changes which occur in the muscles, the reaction of which can be demonstrated by biopsy.

DR STEPHAN EPSTEIN, Marshfield, Wis I agree with Dr O'Leary that this is the chronic type of disseminated lupus erythematosus I thought that the lesions in this woman were also interesting from a morphologic point of view This patient has definite lesions at the tips of the fingers Usually one considers these lesions as an indication of the subacute or acute form In this case the patient does not present signs of a subacute eruption If one looks closely at the eruption of the fingers it will be seen they are a little different from the erythematous lesions which are usually found in this location This patient shows definite tiny hyperkeratoses and telangiectases at the terminal phalanges of the fingers This picture corresponds to the lesions in chronic lupus erythematosus and seems to be rare I remember only 1 other case in which I have seen similar lesions on the fingers

DR M H EBERT Clinically I thought those lesions on the fingers were interesting It looks as though they had been originally punched out They were suggestive of a syphilitic lesion The patient also had a lesion with punched-out appearance on the nose, which would indicate a destructive action suggestive of lupus vulgaris I think that without lesions on the hands and arms and no biopsy this would have been an interesting differential diagnosis from a clinical point of view

I thought that this was an interesting case from two or three angles, the first of which was the possibility that syphilis is present That is of clinical significance in early acute lupus erythematosus Fifteen or twenty years ago I presented a patient with acute lupus erythematosus with lesions on the finger tips

## NEW YORK ACADEMY OF MEDICINE, SECTION OF DERMATOLOGY AND SYPHILIS

DAVID BLOOM, M D, *Chairman*

GEORGE M LEWIS, M D, *Secretary*

*Feb 1, 1944*

### A Case for Diagnosis (Psoriasis?) Presented by DR E W ABRAMOWITZ

C S, a woman aged 62, was previously presented at the New York Academy of Medicine, Section of Dermatology and Syphilis, on Jan 4, 1944

Biopsy of a lesion on the left elbow was reported as indicative of psoriasis, while biopsy of a lesion on the face was reported as indicating lupus erythematosus The results of a urinalysis were normal, and the Wassermann reaction of the blood was negative

The patient has received numerous injections of liver extract and injections of bismuth subsalicylate without benefit Since the application of ammoniated mercury and salicylic acid ointment to the eruption on the face, the eruption has improved considerably

#### DISCUSSION

DR E W ABRAMOWITZ This patient was presented in January 1944 on account of the eruption on the face which closely resembled lupus erythematosus However, she had some lesions on the elbows and one lesion on a buttock which looked more like psoriasis The eruption was of comparatively short duration, and she gave a history of having had a similar outbreak about four or five years previously, it had disappeared after a few injections of a bismuth preparation The histo-

pathologic examination of the lesion on the face was reported as indicating lupus erythematosus I believe that I said at that time that I was not sure whether she had lupus erythematosus of the face and psoriasis of the body or whether it was psoriasis in both areas With use of ammoniated mercury and salicylic acid ointment the eruption on the face is less conspicuous I believe that there was a biopsy from the lesion on the body, which showed psoriasis Dr Sachs still insists that the histologic picture of the lesion on the face is typical of lupus erythematosus Nevertheless, I believe now that the whole eruption is psoriasis Dr Rosen concurs in this opinion

DR ISADORE ROSEN This case illustrates the fallacy of making a diagnosis of lupus erythematosus just because the patient has symmetric lesions on the face Psoriasis limited to the face is sometimes mistaken for lupus erythematosus In this particular patient there were one or two lesions of psoriasis on the trunk, a fact which helps in differential diagnosis

DR LOUIS CHARGIN If this patient did not have an eruption on the body I wonder whether it would be so easy to make the diagnosis of psoriasis I cannot make a diagnosis in this case I do not know what the lesion on the face is There are some points in favor of lupus erythematosus and some in favor of psoriasis Likewise it lacks some of the essentials of each A positive diagnosis of psoriasis is difficult to make if one examines the lesions on the face One should try if possible to fit all the lesions into one disease entity From the appearance of the lesions on the arm, one would make a diagnosis of psoriasis I think that perhaps another biopsy might clear up the difficulty, since the pathologist has made the diagnosis of lupus erythematosus

DR PAUL GROSS The statement by Dr Rosen that the location of dermatologic lesions should not be a criterion in making a diagnosis deserves special indorsement in this case On the other hand, the presence of psoriatic lesions on the body does not exclude the possibility that the facial eruption is lupus erythematosus To settle the question, the eruption on the face should be further treated with topical applications suitable for psoriasis If there is no response, another biopsy will be necessary to confirm the diagnosis of lupus erythematosus

DR OSCAR L LEVIN I cannot make a positive diagnosis on this examination However, from examination of the lesions, certain diseases are suggested First, on the face, seborrheic dermatitis, which I do not think it is, comes under consideration because of the distribution and other factors Psoriasis resembles it It also suggests lupus erythematosus, but the usual characteristics are absent The eruption of the face if seen alone, makes one think of avitaminosis I do not know whether the patient suffers from avitaminosis, but I should like to try large doses of vitamin B complex, riboflavin especially The lesion on the back of the left elbow suggests psoriasis It could be psoriasis, but I do not think that it is, because the patch is made up of pinhead-sized and slightly larger, elevated papules of a reddish color on an inflammatory base and the scaling is not that of psoriasis There are not the bleeding points of psoriasis Clinically I do not believe the papules are those of psoriasis Lupus erythematosus is readily excluded The report on the pathologic change of the lesion on the elbow I believe indicates psoriasis

The patch on the left buttock is fairly sharply circumscribed, not so red as the lesion on the face but slightly darker than that on the elbow and shows none

of the characteristics of lupus erythematosus and none of the signs of psoriasis. If I were required to make a diagnosis to explain the whole picture, I should make a diagnosis of erythroderma and small nodular sarcoid of Boeck. This should be confirmed by a negative reaction to tuberculin and the results of further study of the pathologic conditions.

**DR E W ABRAMOWITZ** Some authorities say that the histologic picture of lupus erythematosus is not definite. Pathologists once in a while report eruptions of lichen planus and other dermatoses as lupus erythematosus, and they report lupus erythematosus as other dermatosis. If this is lupus erythematosus of the face, it certainly has developed rapidly in the short time the patient has had the eruption. She has an isolated patch on the buttock and patches on the elbows that apparently are psoriasis. She has no lesions on the scalp or elsewhere on the body to help in the diagnosis of psoriasis.

**DR DAVID BLOOM** Frequent observation of the patient made me change the diagnosis from lupus erythematosus to psoriasis. Injections of a bismuth preparation and of liver extract were of no benefit, but the eruption responded remarkably to the application of ammoniated mercury and salicylic acid ointment.

**A Case for Diagnosis (Ephedrine Eruption? Lichen Planus?)** Presented by **DR E W ABRAMOWITZ**

**W J**, a woman aged 71, was previously presented at the Manhattan Dermatological Society, on Jan 11, 1944, although the case was not included in the published transactions of the society.

The patient was first seen at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Dec 27, 1943, complaining of an eruption of three months' duration. From October 27 to December 20, she had been receiving from a private physician drops containing zinc sulfate, and ephedrine, for an inflammation of the eyes. About one month after she started to use the drops, the eruption appeared on her face and later extended to the upper extremities.

The face shows symmetrically a fairly well defined, brownish red plaque, and a similar plaque is seen on the left buttock. On the extensor surfaces of the upper extremities, there is a papular eruption of bluish red color.

A patch test with the eye drops elicited a negative reaction. Urinalysis gave normal results. The Wassermann reaction of the blood was negative. The blood count was normal. Biopsy of a specimen taken from a lesion on the back of the forearm was reported as showing a toxic dermatitis (possibly drug eruption).

**DISCUSSION**

**DR E W ABRAMOWITZ** This is another case which has presented difficulties from the standpoint of clinical diagnosis. The patient was presented previously at the Manhattan Dermatological Society as possibly having a drug eruption due to ephedrine. She had been using drops containing that drug. The eruption was much more conspicuous on the face at that time than it is now. On the arms it was about the same as it is at present. The impression that one gets on examining the patient's arms now without looking at the face is that she has acute lichen planus, even though it is distributed on the extensor surfaces. She has no itching, and there are no lesions in the mouth. A biopsy was made from one of the lesions on the arm. There was no histologic picture of lichen planus, only a rather

uniform plasma cell infiltration in the upper part of the corium with some changes in the blood vessels and nothing else. Dr Sachs came to the final conclusion that the best diagnosis he could offer was some sort of toxic eruption due to a drug. The eruption on the face is clearing. It has left behind considerable pigmentation. The few scattered lesions on the body are clearing, but the eruption on the arms has remained about the same except that some of the papules have a linear arrangement. There are a few that show an annular arrangement. Some of my associates and I feel that it is not a classic lichen planus. I have seen eruptions of this type that defy definite classification for some time until finally the patient begins to show manifestations of Hodgkins' disease or of some other type of lymphoblastoma.

**DR ISADORE ROSEN** I think that the lesions on the face and upper extremities are of the same causation. My clinical diagnosis is toxic erythema now in the process of repair. When I first saw this patient at the clinic, the features were much more characteristic of a toxic eruption than they are this evening.

**DR G F MACHACEK** From what I saw I should say that this is not lichen planus but some more deeply seated, inflammatory, tiny granulomatous infiltration. I did not study it in its finer details. I suggest investigation from the standpoint of the cholesterol content of the blood. It is possibly xanthoma diabeticorum. I have seen such lesions which did not look much different under the microscope.

**DR EUGENE TRAUGOTT BERNSTEIN** On the ground of the morphologic attributes I should exclude lichen planus. There is no umbilication. The single lesions do not show polygonal outlines. The symmetric distribution on the extremities, the raised lesions and the distribution on the face and extremities together show the picture seen in erythema multiforme of toxic origin. I agree with the others that this is a toxic eruption but there is one feature which is striking, the patch on the buttocks with pigmentation to an extent which impresses me as poikiloderma vasculare (Civatte) as seen on the anterior aspect of the neck and chest. I think that the clinical appearance is not at all like that of lichen planus, and the diagnosis of a toxic eruption should be accepted.

**DR MABEL SILVERBERG** The patient had all her teeth extracted on one day and the eruption appeared not long afterward. I think that that sort of trauma can cause this type of eruption.

**DR E W ABRAMOWITZ** The eruption did not fit into any group of sarcoid even though it might turn out to be some form of tuberculid. There have been a good many diagnoses suggested. As for toxic eruption from a drug, of course I know that ephedrine produces many kinds of eruptions, as do other drugs for that matter. The patient has not had any other medicine, like arsenic, that I know of. That type of eruption after arsenic might persist for such a length of time, but still it would not give an almost pure plasma cell infiltration which this section shows. We are trying to make some hematologic studies to see if they will help in making the diagnosis. The patient has not been fully cooperative.

**Exfoliative Dermatitis** Presented by **DR CHARLES WOLF**

**H P**, a Negro boy aged 10, states that in April, 1943, a scaldiness first appeared on the scalp and was followed within a week by a generalized eruption con-



sisting of pinhead-sized erythematous papules. Within a short time the eruption changed into an erythrodermic scaly dermatitis. There is a generalized erythroderma with a fine desquamating scale and involvement of the soles and palms as well as the nails.

Examination of the urine for arsenic showed a slight trace. The Wassermann reaction was negative. A hematologic examination showed 70 per cent hemoglobin, 3,500,000 erythrocytes and 3,888 leukocytes.

## DISCUSSION

DR PAUL GROSS: This boy has a generalized erythroderma, to give the eruption a descriptive name. The interesting features are scaling of the scalp, hyperkeratosis of the palms and soles and a somewhat rough appearance of the erythematous skin. For this reason I believe that this is a pityriasis-rubra-pilaris-like eruption as occasionally observed in children. I have found that this dermatosis responds to parenteral injection of liver preparations and oral administration of vitamin A.

DR OSCAR L. LEVIN: I think that this eruption is due to ingestion of arsenic. The patient has an almost universal erythema with inflammatory changes and secondary exfoliation. For treatment I advise plenty of fluids, rest, the search for and exclusion of arsenic ingestion and the use of a bland ointment for the skin. It will take months to cure the eruption. I think, in an individual of this age with a generalized eruption of this type, arsenic dermatitis should be excluded.

DR LOUIS CHARGIN: I cannot offer a diagnosis in this case but I should like to second the views of Dr. Gross that we are perhaps dealing here with the so-called pityriasis rubra pilaris. I have seen this in younger children. I recall a child of 4 years with a similar eruption which was not true pityriasis rubra pilaris but presented a picture much like it. The therapeutic suggestions made by Dr. Gross are good, but if they are left alone these patients get well.

DR OSCAR L. LEVIN: On what grounds is the diagnosis of pityriasis rubra pilaris made?

DR PAUL GROSS: As I said before, this is an erythroderma and there is no extensive exfoliation present. There is rather an accentuation of the follicles. In the absence of typical follicular plugging on the dorsum of the fingers, I prefer to call this condition a pityriasis-rubra-pilaris-like eruption rather than pityriasis rubra pilaris. If, as Dr. Chargin said, a patient like this may get well in the hospital without vitamin therapy, then this is due to an improvement in nutrition. The same holds true for typical vitamin deficiencies, provided they have not progressed too far.

DR DAVID BLOOM: I favor the diagnosis of pityriasis rubra pilaris. If the patient had had a few follicular keratotic papules on the backs of his fingers hardly any one would have disputed this diagnosis.

DR CHARLES WOLF: I want to disillusion any one who thinks this is pityriasis rubra pilaris. While in the hospital he received good medical care and became worse. There was no involvement of the hair follicles at any time. It was a papular eruption in the inter-follicular spaces. Perhaps pityriasis rubra of Hebra may be considered. To sum up, I think this is a case of exfoliative dermatitis of the Brock-Wilson type. Whether ingestion of chemicals is an etiologic factor in this case one cannot definitely state.

DR PAUL GROSS: After the rather vehement expression of opinion by Dr. Wolf, I believe this patient should be presented again after he has received treatment with liver and vitamin A.

### Erythroderma Ichthyosiforme Congenitale Presented by DR ISADORE ROSEN

A R., a man aged 22, was admitted to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Dec. 13, 1943, with an eruption on the body which has been present since birth. The skin on the trunk and extremities is considerably thickened, dry and scaly. The lower part of the back and the lower two thirds of the trunk anteriorly show much more intense involvement than the upper third of the trunk. The palms and soles are hyperkeratotic. The nails are thickened. The scalp is dry and scaly.

The patient's two brothers and one sister are normal. Neither of the parents has an abnormal skin. The parents are not related to each other. The patient states that he does not perspire at all except on the face and scalp. He feels, therefore, extremely uncomfortable in the summer.

The urine was normal. The Wassermann reaction was negative. Microscopic examination showed considerable hyperkeratosis, considerable acanthosis and moderate cellular infiltration in the upper part of the cutis.

## DISCUSSION

DR ADOLPH ROSTENBERG: While I fully agree with Dr. Rosen, there are some features missing. A striking feature in a patient of mine, an 18 year old woman, was redness of the face, it was extremely red and congested, and the ichthyotic condition was more in plaque form, distributed on the extremities. Yet, I suppose the disease is so rare that one does not see the same features in every case.

Dr. E. W. Abramowitz, Dr. Max Scheer and Dr. Oscar L. Levin agreed with the diagnosis as presented.



## Correspondence

### PREVENTION OF IMMEDIATE NAUSEA AND VOMITING FOLLOWING ADMINISTRATION OF NEOARSPHENAMINE

*To the Editor* —During my experience at the Erlanger Hospital Venereal Disease Clinic, in Chattanooga, Tenn., with many hundreds of patients being treated for syphilis, I found that many complained of nausea and vomiting immediately after the intravenous injection of neoarsphenamine. The nausea and vomiting were severe enough to deter them from continuing their treatments, with the result that there were many delinquents because of this reaction. Most of these patients continued to have nausea and vomiting even after inapharsen was substituted for neoarsphenamine.

I interrogated the reacting patients regarding their symptoms, and they all agreed that the nausea and vomiting were caused by the odor and taste of the drug immediately after the start of the injection and before it was completed.

Several different measures were tried to control this, like chewing gum, smoking a cigaret, pinching the

nostrils together, smelling perfume from a handkerchief to the nose while the injection was being given, abstaining from food for two hours before the injection and others. None of these measures were effective.

I concluded that if I could temporarily anesthetize the taste buds on the tongue, and thus abolish taste sensation, it would prevent reflex nausea and vomiting. I tried this with the patients who were routinely assigned to me and who complained of nausea and vomiting.

Before these patients received their intravenous injection, I gave them 2 tablets containing ethyl aminobenzoate ( $\frac{1}{4}$  grain [0.015 Gm.] each) with instructions to place both tablets on the tongue and to keep them on the tongue until the tablets were dissolved. After treatment, they reported back to me before leaving the clinic. In each instance I was informed by a smiling and grateful patient that there was no nausea or vomiting. The vomiting patients refused to take their subsequent treatments without seeing me first and obtaining the tablets. I treated several hundred patients with these tablets, with success in every case, surprising as it may seem.

HAROLD W. SEFF, M.D., Delaware, Ohio

## ULCERATIVE HODGKIN'S DISEASE AND LYMPH NODE IMPRINTS

S E SWEITZER, M.D., AND L H WINER, M.D.

MINNEAPOLIS

Cases of Hodgkin's disease with cutaneous manifestations have previously been studied with the usual fixation technic of the skin and node tissue. We wish to report the great value of node and skin imprints in the study of this disease. The frequency of cutaneous involvement has been given by different authors as varying from 16 per cent (by Barron<sup>1</sup>) and 29 per cent (by Wallhauser<sup>2</sup>) to 38 per cent (by Goldman<sup>3</sup> and Cole<sup>4</sup>). Miller<sup>5</sup> has mentioned that these manifestations are of two types, the nonspecific and the specific. The nonspecific manifestations, lacking the characteristic histopathologic changes, include diverse conditions ranging from generalized pruritus, lichenification, urticaria, prurigo-like nodules, bullous eruptions, exfoliative erythrodermas and pigmentation to loss of hair and changes in the nails. They have also been labeled as "ids" or lymphogranulids by Nanta and Chatellier<sup>6</sup>. The specific lesions, those having a histologic appearance characteristic of Hodgkin's disease, show localized or disseminated infiltrations and may resemble prurigo nodules or gummas. They may be deep or superficial, pruritic, ulcerated or secondarily infected.

Among the specific manifestations of Hodgkin's disease is ulceration. This is comparatively rare. Senear and Caro<sup>7</sup> in a recent paper stated that ulceration in Hodgkin's disease is of three types: (a) Giosz and Hirschfield type, cutaneous nodules which ulcerate, (b) Cole-Alderson type,

in which there is extension from lymph node, bone or other tissues, and (c) Doessekkei-Kren-Saalfeld type, in which the skin is the primary focus of Hodgkin's disease. Therefore of the three types, the first is ulceration of limited extent developing in small nodules in the skin, whereas the second and third forms consist in extensive ulceration either by extension from an underlying involved structure or from large infiltrations in the skin without involvement of the underlying structure.

The rarity of specific lesions in the skin has recently been emphasized by Kierland and Montgomery,<sup>8</sup> who reported the finding of a typical histologic picture in Hodgkin's disease in only 3 of 300 cases of cutaneous lymphoblastoma.

Difficulty in the diagnosis of Hodgkin's disease of the skin has been mentioned by practically every author. This is well illustrated by the case of Kren,<sup>9</sup> in which a patient was given a diagnosis of sarcoma and an amputation of the leg was performed, only at autopsy, four years later, was Hodgkin's disease diagnosed. Howard Fox<sup>10</sup> mentioned the difficulty in differentiating Hodgkin's disease from mycosis fungoides. Goeckerman and Montgomery,<sup>11</sup> in a report of 2 unusual cases, mentioned the same difficulty in diagnosis. More recently, Reimann, Havens and Herbut<sup>12</sup> discussed a case in which the diagnosis of Hodgkin's disease was established only at autopsy. In this case, relapsing febrile nodular panniculitis was suspected during life.

## REPORT OF A CASE

A. E., a married man aged 47, was admitted to the Minneapolis General Hospital on Sept. 3, 1942 because

From the Division of Dermatology, University of Minnesota, and the Minneapolis General Hospital.

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5 Miller, H. E. Lymphogranulomatosis Cutis, *Arch. Dermat. & Syph.* **17**: 156-181 (Feb.) 1928.

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8 Kierland, R. R., and Montgomery, H. Hodgkin's Disease, *Proc. Staff Meet., Mayo Clin.* **16**: 124-128, 1941.

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10 Fox, H. Lymphogranulomatosis of the Skin in Hodgkin's Disease, *Arch. Dermat. & Syph.* **2**: 578-593 (Nov.) 1920.

11 Goeckerman, W. H., and Montgomery, H. Cutaneous Lymphoblastoma. Report of Two Unusual Cases, *Arch. Dermat. & Syph.* **24**: 383-395 (Sept.) 1931.

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of swelling of the left inguinal lymph nodes and numerous purulent ulcers on the anterior surface of the left thigh. These lymph nodes first became swollen in July 1941 and receded in a few weeks. However, in September 1941 the same lymph nodes enlarged again, and the enlargement persisted to the time of his admission to the hospital. In May 1942 a small nodular itching eruption developed on the anterior surface of the left thigh, and because of the itching the patient picked and scratched the nodules until they formed open ulcers. The patient was able to continue work until his admission to the hospital, noticing only edema of the left leg during the day, which cleared up after a night's rest in bed. He was treated by several physicians with no success until one physician finally told the patient that he had a cancer and should go to the hospital. He had lost 8 pounds (3.6 Kg) between the onset of the illness and the time of admission to the hospital, and he attributed this loss of weight to his hard work. His past history revealed nothing significant except for the fact that he had been told that he had draining left inguinal nodes as an infant and they had healed by the time he was 2 years of age.

lesions formed on the sites of the scars, and subsequent therapy in the next three months, totaling 1950 r through 1 mm of aluminum, was without effect.

The patient remained in the hospital from September 3 to December 18, at which time he went home, but he returned on December 31 and remained in the hospital until his death, on June 17, 1943.

His temperature varied from 98 to 99 F until March 26, 1943, when it rose to 100 F. The temperature then returned to normal for two days, after which it rose again to 100 F. Beginning on April 18, the patient's temperature rose daily to 99 F and at times as high as 101 F until June 11, 1943, at which time it was from 97.6 F low to 99 F high daily.

Hematologic examinations, made many times, showed hemoglobin contents varying from 83 to 98 per cent red cells from 4,300,000 to 4,600,000 and white cells from 11,500 to 21,000, the differential white cell count revealed 80 to 90 per cent polymorphonuclear leukocytes, 10 to 16 per cent lymphocytes, 1 to 8 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils. The size and shape of the red blood cells were normal and the white blood cells were toxic. The urine was



Fig 1—Medial and posterior portions of the left thigh, showing multiple confluent ulcers in Hodgkin's disease of the skin.

On examination the patient was observed to be a well nourished and well developed man not acutely ill. The following abnormal conditions were observed: There was a scar 5 cm long parallel with and 2 cm below Poupart's ligament on the left side (this was a result of the draining nodes in infancy). The inguinal lymph nodes on both sides were enlarged to about 3 cm in diameter. They were hard and adherent to the skin on both sides. On the anterior and the medial surface of the entire left thigh were numerous ulcers from 1 to 3 cm in diameter. These ulcers began as small papules which disintegrated and eroded; they then became larger and coalesced and showed no tendency to spontaneous healing. They were freely movable on the underlying subcutaneous structures and were only slightly tender. They had elevated, indurated sharply defined borders and granulating purulent covered bases. Some of the smaller ulcers were covered with brownish crusts on the surface. The removal of these crusts showed ulcers with granulating purulent bases. Interspersed between the ulcers were several nonulcerated papules.

Roentgen therapy was instituted on Nov 24, 1942, being given to the inguinal nodes and ulcers. The first dose was 300 r filtered through 1 mm of aluminum, and the subsequent doses at weekly intervals varied from 150 to 200 r through 1 mm of aluminum. At first this therapy caused the ulcers to heal, but new

normal, the Wassermann reaction of the blood was negative, and the sedimentation rate was 50 mm sixty minutes. A Frei test elicited a negative reaction for lymphogranuloma venereum.

Smears and cultures from the ulcer bases were negative for yeasts and fungi. However, diphtheroid bacilli *Staphylococcus albus* and gram-positive streptococci were found on the culture, but no hemolytic streptococci or diphtheria bacilli were found.

A biopsy of the border of an ulcer on the left thigh was performed Sept 9, 1942. Histologic sections were prepared and stained with hematoxylin and eosin. On microscopic examination, the epidermis at the border of the ulcer was seen to be practically unchanged except for the tendency of flattening of the epidermal pegs due to the pressure from the dense infiltrate in the cutis. In the papillary portion of the cutis, the infiltrate was essentially serous, and the blood capillaries in the papillary bodies were dilated and contained numerous eosinophils, a few lymphocytes and red blood cells. The connective tissue of the papillary portion stained poorly with eosin and appeared edematous and even vacuolated, so much so that the cell had the appearance of having a small round nucleus surrounded by a vesiculated nonstaining cytoplasm.

The greatest changes were in the upper and middle portion of the reticular cutis. The lower portion of

the reticular cutis, directly over the subcutaneous fat, was practically uninvolved. The changes were most evident in areas surrounding zones of liquefaction necrosis, which were closely surrounded by dense cellular infiltrate of lymphocytes, polymorphonuclear neutrophils and many eosinophils. Adjacent to these cells with relatively small nuclei were cells with large nuclei containing large nucleoli and vacuolated cytoplasm. These cells looked like reticulum cells. Some of the cells had nuclei undergoing mitosis. Others were larger and multinucleated as a result of amitotic division and had the characteristics of Sternberg-Reed giant cells. Interspersed in several areas in an irregular fashion were bundles of recently formed connective tissue which still contained many fibroblasts.

Histologically, this section was diagnosed ulcerative Hodgkin's disease of the skin.



Fig 2—More recent small nodules and ulcers of Hodgkin's disease on the right thigh and inguinal region.

A biopsy of the right inguinal lymph node was performed on Sept 18, 1942. The histologic sections of the lymph node showed almost complete obliteration of the normal structure. The capsule was increased in thickness and was composed of dense fibrous connective tissue. The follicles, normally consisting of compact conglomerations of lymphocytes, were practically replaced by the larger-celled masses of proliferated reticulum and newly formed congested blood capillaries. Areas of liquefaction necrosis of irregular outline were noted in several areas, and these were surrounded by a bordering zone of small lymphocytes. This proliferating reticulum consisted of cells with large nuclei and nucleoli which were definitely characteristic of Stern-

berg-Reed cells. These cells appeared to be lying free in the tissue, unattached. Several of the nuclei showed mitotic figures. Interspersed among these cells were numerous eosinophils. This section was also diagnosed Hodgkin's disease.

A node imprint, according to the technic advocated by Schleicher,<sup>13</sup> showed the Sternberg-Reed cells to be much more typical than they were in the tissues. These cells were characterized by their fine granular cytoplasm and large nucleus containing an extremely large nucleolus.

The technic of making a node imprint is as follows. An excised or punched-out, unfixed specimen is cut in two and compressed in a forceps. The exuding surface is touched lightly on a clean glass slide. The slide is then dried by rapid fanning a few minutes and then stained immediately. The staining technic is performed in the following manner, according to Schleicher:

- (a) Apply 0.5 cc of Wright's blood stain (0.1 Gm of stain in 60 cc of pure methyl alcohol) and allow to act on the imprints two minutes.
- (b) Dilute the dye on the slide with 2 cc of distilled water ( $pH$  6.4), mix well and allow to stain for ten minutes.
- (c) Wash off the diluted stain with distilled water and check differentiation under the microscope.
- (d) Differentiate by dipping the slide for one to three seconds in Schleicher decolorizer.
 

Distilled water	100 cc
Pure methyl alcohol	5 cc
Acetone	0.5 cc
- (e) Rinse in distilled water and allow to dry in air.

On Oct 8, 1942, a sternal puncture and smear showed no abnormal cells.

**Autopsy**—The body was poorly nourished. There was slight pitting edema of the legs and an intense edema of the scrotum. The anterior and medial portions of the left thigh were covered with irregular confluent crusted ulcers. The ulcers on the medial surface of the left thigh extended around and involved the left buttock. There were also numerous firm elevated nodules about 1 cm in diameter in the skin of the right hip, upper part of the thigh and inguinal region. The remainder of the skin was uninvolved. Microscopically, the ulcers of the skin showed necrosis with polymorphous cellular infiltration, Sternberg-Reed giant cells, plasma cells and fibroblastic proliferation. The nonulcerated nodules showed essentially the same characteristics without the areas of necrosis. These cutaneous lesions were diagnosed Hodgkin's disease on microscopic examination.

The right pleural cavity contained 1,000 cc of pink fluid, and the left pleural cavity contained 3,000 cc of similar fluid. The right lung weighed 710 Gm and the left lung 420 Gm. On gross section, the lungs showed moderate congestion and edema of the lower lobes. No areas of actual consolidation of the lungs were found.

The spleen was smooth and on the cut surface showed several white areas up to 4 mm in diameter, which on microscopic examination were seen to consist of reticulum hyperplasia and fibrosis. The liver, kidneys and adrenals showed no gross or histologic changes.

The lymph nodes were generally enlarged, some up to 2 cm in diameter, and were seen to be of white fleshy nature. Especially enlarged were both the inguinal and the axillary lymph nodes as well as those in the mediastinum and mesentery. The mesenteric

<sup>13</sup> Schleicher, E. M. Staining Aspirated Bone Marrow with Domestic Wright's Stain, *Stain Technol* 17:161-164, 1942, personal communication to the authors.

nodes were fused around the lower 8 cm of the aorta and inferior vena cava and extended along both common iliac vessels and tended to compress them. A few similarly enlarged lymph nodes, up to 1 cm in diameter, were found in both sides of the neck.

Lymph nodes from the mediastinum and inguinal region on microscopic examination showed obliteration of their normal structure and replacement by hyperplastic reticulum. The postmortem diagnosis was ulcerative Hodgkin's disease of the skin, bronchopneumonia and bilateral pleural effusion.

derma was offered as a diagnosis by two of the members. For histologic diagnosis a microscopic section of skin from the border of one of the ulcers was shown to four members of the pathology department of the University of Minnesota, and four different diagnoses were offered namely, Hodgkin's disease, malignant lymphoblastoma, lymphosarcoma and malignant melanoma. A microscopic section of a lymph

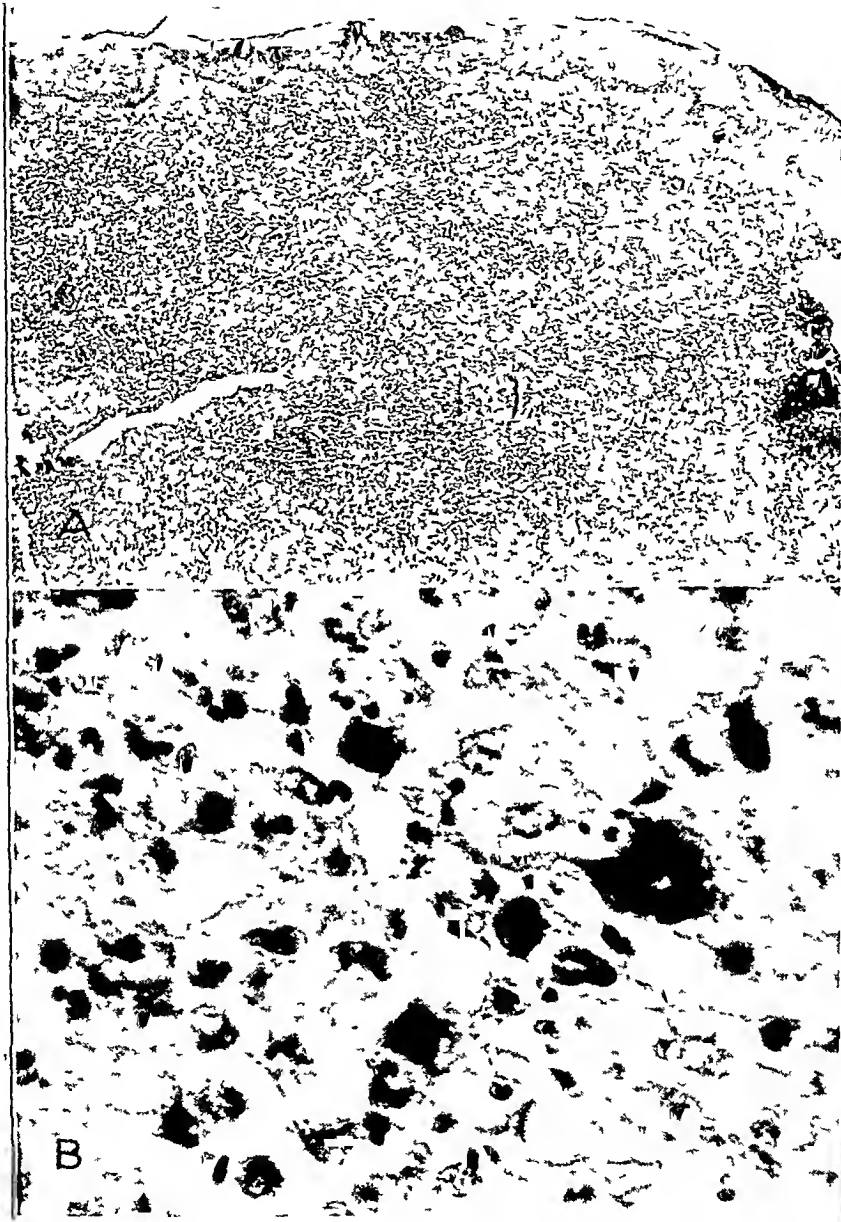


Fig 3—A, photomicrograph of skin, showing infiltration and necrosis at the edge of an ulcer in Hodgkin's disease. Hematoxylin and eosin,  $\times 40$ . B, blocked-out zone in fig 3, showing Sternberg-Reed giant cells and mitotic figures. Hematoxylin and eosin,  $\times 450$ .

#### COMMENT

Clinically, this case of ulcerative Hodgkin's disease presented difficulties in diagnosis. The patient was presented before the Minnesota Dermatological Society at the meeting of Nov 13, 1942 (ARCH DERMAT & SYPH 48: 104 [July] 1943) with the diagnosis of ulcerative Hodgkin's disease, and in the discussion that followed pyo-

node was shown to these pathologists, who suggested the following diagnoses: Hodgkin's disease, malignant lymphoblastoma and lymphosarcoma.

The node and tissue imprints, which were of great help to us, were first used in the diagnosis of Hodgkin's disease of the skin by Nanta and Chatellier.<sup>6</sup>

The essential characteristic of Hodgkin's disease histologically is the Sternberg-Reed giant cells, rich in clear, practically nonstaining, hydropic cytoplasm, having a large round, oval or lobulated nucleus containing one or more large, easily visible nucleoli. In the more acute forms of the disease, these cells show only a

infiltrate is characteristic of Hodgkin's disease, together with the tendency toward formation of fibrosis. The infiltrate consists of lymphocytes, polymorphonuclear leukocytes, plasma cells, fibroblasts and eosinophils. Arndt,<sup>14</sup> Bell<sup>15</sup> and others have laid most stress in the histologic diagnosis on the polymorphism of the infiltrate

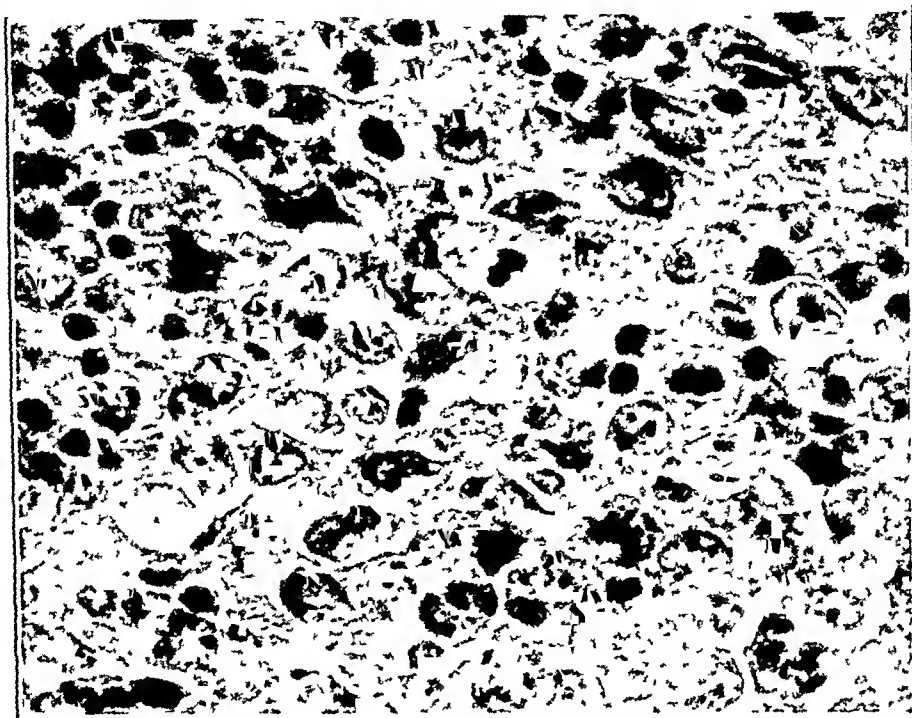


Fig 4—Photomicrograph of lymph node, showing the replacement of the lymph follicle by proliferative reticulum. Note the numerous mitotic figures in the Sternberg-Reed cells. Hematoxylin and eosin,  $\times 600$ .

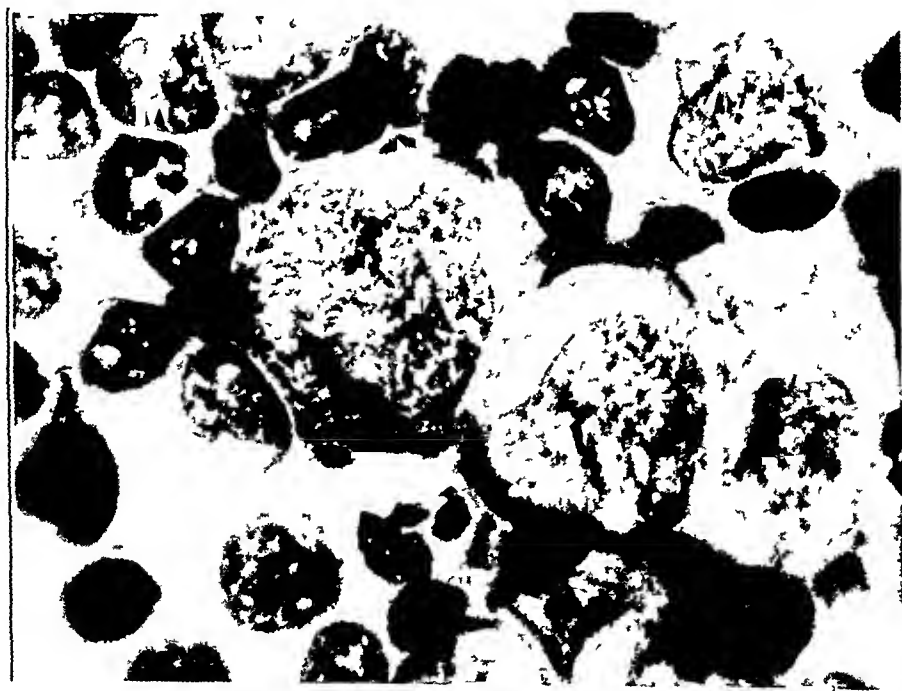


Fig 5—Lymph node imprint with two Sternberg-Reed cells in the center. The larger of the two cells shows the large nucleus. Schleicher's stain,  $\times 1,800$ .

single dark nucleus rich in chromatin or even numerous cells containing nuclei undergoing mitosis. In the more chronic forms the cells are multinucleated, having undergone amitotic division of the nucleus. Besides Sternberg-Reed cells, which are in our opinion, reticulum cells undergoing proliferation polymorphism of the

rather than on the finding of Sternberg-Reed cells

14 Arndt, G. Beitrag zur Kenntnis der Lymphogranulomatose der Haut, *Virchows Arch f path Anat* 209 432-452, 1912.

15 Bell, E. T. Text-Book of Pathology, ed 5, Philadelphia, Lea & Febiger, 1944, p 318.



This case could be classified in the group of cases of the Glosz and Hirschfeld type of the disease, of which the lesions are cutaneous nodules which ulcerate.

Our experience with roentgen therapy was not a happy one in this case. We had an early improvement of the cutaneous lesions, which, however, later recurred and became refractory to subsequent roentgen therapy.

#### DIFFERENTIAL DIAGNOSIS

It is often difficult to differentiate Hodgkin's disease from mycosis fungoides, leukemia and lymphosarcoma, and this is essentially the reason for their inclusion by some writers in one large

chronic forms, which infiltrate the skin with the formation of nodules, leukemias can at times look like nodules of Hodgkin's disease. However, leukemias do not ulcerate as a rule, and the concomitant blood picture is diagnostic. The leukemias on histologic section show uniform monomorphous cell tumors. One does not see the proliferation of connective tissue observed in Hodgkin's disease. In monocytic leukemia, the histologic differential diagnosis would have to be based on the differentiation of the histiocyte, with its phagocytosing properties and its extremely irregular cytoplasm, from the Steinberg-Reed cell, which does not have the phagocytosing property. Also, in monocytic leukemia the preponderance of monocytes in the blood is characteristic.

Hodgkin's disease and mycosis fungoides may be difficult to differentiate, as is evidenced by the frequent clinical diagnosis of mycosis fungoides which is changed to Hodgkin's disease on histologic examination or at autopsy. Mycosis fungoides is a disease of the skin primarily whereas Hodgkin's disease is primarily a disease of the reticulum of the hemopoietic organs, namely, lymph nodes, spleen and liver. Both diseases are granulomas, and we agree with Senear<sup>16</sup> that clinically in various stages mycosis fungoides and ulcerative Hodgkin's disease may resemble each other.

Histologically, mycosis fungoides is characterized by multiplicity of cell infiltrate, pyknosis, karyorrhexis and nuclear clumping in the cellular infiltrate. Thus nuclear and protoplasmic detritus is not seen in Hodgkin's disease. In mycosis fungoides, the lesions disappear by absorption without caseation, in Hodgkin's disease, regression is by caseation and necrosis. Arndt<sup>14</sup> found giant cells of mycosis fungoides simulating those of Hodgkin's disease, but these cells are found in the infiltrative stage of mycosis fungoides and not in the tumorous stage. In the tumorous stage of Hodgkin's disease, large numbers of Steinberg-Reed cells are to be found. In the eczematoid or infiltration stages of mycosis fungoides, pleomorphism of the cell infiltrate is most pronounced, whereas in the tumorous stage the infiltrate is composed essentially of lymphocytic elements and connective tissue granulation cells. In the tumorous stage, the lymph nodes and internal organs contain large numbers of eosinophils, which is not the characteristic in the tumorous stage of Hodgkin's disease. Lapiere<sup>17</sup> stated the belief that both diseases develop from

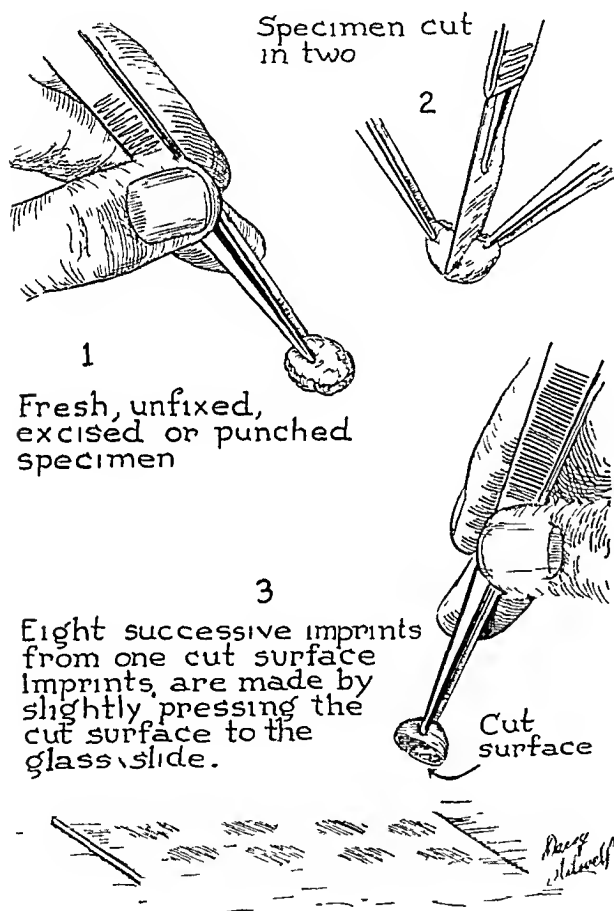


Fig 6—Technic of tissue imprints

group termed lymphoblastoma. Others have expressed the belief that Hodgkin's disease, mycosis fungoides and lymphosarcoma are biologically, morphologically and clinically variants of the same disease. However, we are in accord with Wallhauser<sup>2</sup> and others that in the absence of known etiologic agents adherence to strict histologic distinction should be maintained.

The leukemias, which clinically may be characterized by enlarged lymph nodes not unlike Hodgkin's disease in the acute forms are frequently accompanied with severe purpura, but in the

16 Senear, F. E. Lymphoblastoma Cutis, *M. Clin. North America* 26: 1-12, 1942.

17 Lapiere, S. Etude comparative du mycosis fungoïde et de la maladie de Hodgkin, *Rev. belge sc. med.* 10: 159-171, 1938.

reticuloendothelial tissue and pursue an identical course to the stage of the histiocyte, from this stage, either the mycotic cell of mycosis fungoides or the Sternberg-Reed cell of Hodgkin's disease is formed. We disagree with this statement only so far as it concerns the ability of the histiocyte to change into a Sternberg-Reed cell. In our opinion, the histiocyte can form only a plasma cell or a phagocytic cell whereas Sternberg-Reed cells are direct transformations of the reticulum cells and do not undergo a metamorphosis through a histiocyte stage. The characteristic cell of mycosis fungoides is the large, clear, eccentrically mononucleated cell, which apparently develops in situ from the histiocyte and is phagocytic in nature. At no time is there as great a cellular polymorphism in mycosis fungoides as that found in Hodgkin's disease.

The differential diagnosis of Hodgkin's disease and lymphosarcoma is not an easy one. In several cases Hodgkin's disease has been called sarcoma, several writers have stated that there is a definite transformation of Hodgkin's disease to lymphosarcoma, and still others have expressed the opinion that a sarcoma had been engrafted on the inflammatory tissue of Hodgkin's disease. However, one can readily visualize Hodgkin's disease as a precursor of, or a benign form of, the so-called large cell or reticulum cell lymphosarcoma. An occasional mitotic figure in proliferating reticulum is suggestive of Hodgkin's disease of an acute type that is probably leading to early death, whereas numerous mitotic figures and a more monomorphous infiltrate are more suggestive of lymphosarcoma. Lymphosarcoma is further suggested by the disordered, jumbled arrangement of the mitotic reticulum cells and reticulum fibers.

#### SUMMARY AND CONCLUSIONS

A case of ulcerative Hodgkin's disease of the skin was observed.

The conditions observed in a histologic examination of sections of the skin were typical of the specific form of Hodgkin's disease of the skin.

Typical Sternberg-Reed cells were shown in the lymph node imprint.

Occasionally more than one biopsy must be performed and more than one lymph node must be examined to obtain the correct diagnosis.

Hodgkin's disease is a neoplastic disease of the reticulum, most probably a slowly progressive form of the large cell (reticulum) lymphosarcoma.

The photomicrographs were made by Mr. H. W. Morris.

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#### ABSTRACT OF DISCUSSION

DR. F. E. SENEAR, Chicago. I can say nothing about node imprints, since I have had no experience with them. So far as I know, they are entirely new to the dermatologists of the United States. I think Drs. Sweitzer and Winer are to be thanked for calling attention to them.

Certainly the illustrations show how valuable this method would be in many cases of the lymphoblastoma type, in which there is so much difficulty in diagnosis and so much disagreement among pathologists as to just which type of involvement one is dealing with.

I agree with the authors that the difficulties of diagnosis in cases of ulcerative Hodgkin's disease are great, not only from the clinical but from the histopathologic standpoint.

Clinically, I had experience with 1 patient, whose case was reported by Dr. Caro and me. His disease was of the gross ulcerative type, primary in the skin. Later we had another patient with a similar type of disease, with involvement of the neck. Histopathologically, that patient's disease was of Hodgkin's type, but there was also a great deal of lipid material present in the tissues.

Clinically, as Dr. Sweitzer said, there are three types—the three that he discussed—and yet there are certain general characteristics of the ulcerative type of Hodgkin's disease, a tendency to specific localization in the sense that while the lesions may occur at any place in the large majority of cases they occur in the region of the neck or over the upper part of the thorax or near the proximal ends of the extremities, particularly in the axillary region.

There is a patient under observation now at the University of Illinois College of Medicine who has Hodgkin's disease of the skin, not of the ulcerative type, but some of the dermatologists here saw that patient several days ago when she was used—not primarily because of the Hodgkin's disease but because of an ulcer on the leg which was not connected with the Hodgkin's disease—for the examinations of the American Board of Dermatology and Syphilology. This woman presented a number of lesions on the thighs, individual nodules similar to those shown by Dr. Sweitzer today. They had, as often seen on the lymphoblastomatous type of lesion, a peculiar translucency which was such that several of the candidates for certificates made a diagnosis of lymphangioma circumscriptum.

It was readily apparent why this diagnosis was suggested, because several of these lesions were so dense and translucent that the centers looked as though they were distinctly vesicular, and yet there were no vesicles in the picture.

It is entirely conceivable that with this tendency to central elevation and the different consistency, in time these lesions would undergo degeneration and present much the same picture as that displayed by this patient.

With regard to the authors getting four different histologic diagnoses, I had a similar experience recently with a patient who apparently did not have lesions belonging in the lymphoblastoma group. He had a generalized exfoliative dermatitis. Biopsy of a node was done. The specimens were seen by three eminent pathologists. It so happened that Dr. Smith, of Temple University, was visiting here at the time, and he saw them. Our laboratory made an unequivocal diagnosis of lymphosarcoma. Dr. Smith said that it looked to him as though the case would eventually fall in the group of cases of Hodgkin's disease but that he would be unwilling to commit himself at that time as

to the exact type. Still another capable pathologist made a diagnosis of lymphosarcoma.

Since some of these lesions are primary in the skin—that is, the first manifestation of Hodgkin's disease appears in the skin before there is any glandular enlargement—I think it is well worth while that all keep this type of Hodgkin's disease in mind, rare as it is.

I think that Dr Sweitzer and Dr Winer have made an excellent presentation of another case of this unusual manifestation. Certainly, I think that all dermatologists are going to find use for this type of tissue imprint which they have described.

DR HARTHER L KEIM, Detroit. I think that both Dr Sweitzer's and Dr Senear's remarks certainly show the futility of attempting to make a specific and definite, either clinical or histopathologic, diagnosis. In other words, this is an example, again, of clinical mutations, the increasing number of which are evident all through the literature.

In looking over Drs Senear and Caro's report of cases of ulcerative Hodgkin's disease, I am not entirely convinced that all of those cases that they reviewed were instances of Hodgkin's disease. I am wondering whether or not a good many of them were not primarily cases of lymphosarcoma. It is known that mycosis fungoides and Hodgkin's disease frequently terminate in lymphosarcoma. In one's haste as a dermatologist to make a quick, spot diagnosis, I am quite sure that one gives them clinical designations which are not correct.

I have had no experience with the imprint method. It looks to me as if it offers great possibilities, and I think that from now on all who are studying such cases should utilize this simple method of getting such excellent cell imprints.

I was glad to note that Dr Sweitzer agrees that this group of diseases are neoplastic in origin. It seems to me that the burden of the proof now rests on the physicians who deny the genetic relationship and the neoplastic causation of the lymphoblastomas.

DR SAMUEL M PECK, Bethesda, Md. The authors have introduced a method which will be helpful in certain phases of histopathologic studies.

About fifteen years ago I tried to do something similar in order to study epidermal cells without any changes produced by fixation or other procedures. To carry out my studies, ordinary glass slides were prepared by boiling them in a soapy solution. After they had dried, the surface became adhesive, and when placed against a papule on the skin the top of which had been removed, layers of cells could be made to adhere to the slide. A series of such slides gave what amounted practically to serial sections composed of almost one layer of cells.

DR EARL D OSBORNE, Buffalo. I want to comment on a phase of the practical handling of some of these cases that I think is overlooked, or can easily be overlooked, by dermatologists.

Dermatologists are often asked to sit on tumor committees or tumor boards in large city hospitals, and a good many such cases come to the attention of the tumor committee.

Both Dr Sweitzer and, in his discussion, Dr Senear mentioned primary Hodgkin's disease. I think that all should remember that the attitude toward Hodgkin's disease today is that it is a neoplastic disease and always primary somewhere, and that brings up the method of handling.

It has been my observation with a number of cases in the last three or four years that Hodgkin's disease is apt to ulcerate when it is primary in the skin.

I have recently advised wide surgical removal of the lesions of primary Hodgkin's disease when the disease is localized in the neck or of primary Hodgkin's disease of the skin. It was stated last year that at the Memorial Hospital in New York a series of patients now have gone a few years without any further signs of Hodgkin's disease. Evidently it is possible to cure the disease if the primary tumor is completely removed.

DR HENRY E MICHELSON, Minneapolis. Dr Sweitzer's experience is so vast that he can present an iconographic case whenever he wishes. If one looks back through his publications, one will recall that he has reported many most unusual cases, and this is just another example. The method to which he and Dr Winer have called attention is worthy of further use and may possibly solve the problem of early identification of specific lymphoblastoma.

DR FRANCIS W LANCH, St Paul. Dr Sweitzer's lantern slide projections gave striking evidence of the aid to be obtained by study of node imprints. Perhaps many of the members, like Dr Peck, have wondered whether this technic can be applied directly to study of cutaneous lesions. While studying the cutaneous lesions of monocytic leukemia some years ago, I worked with a member of the division of hematology and provided him with specimens made with a large biopsy punch. He cut vertically through the tissue and applied the cut surfaces to glass slides but without much success. Perhaps the method should be studied again.

DR JOSEPH GRINDON SR, St Louis. I believe that, besides the three types of ulcerative Hodgkin's disease that have been described, there is a fourth type.

A patient came under my observation whose case, so far as I know, was unique. She was a woman of 60, who had what was clinically Hodgkin's disease, with enormous involvement of the lymph nodes in the neck and also in the axillas. At no time was there any itching whatever.

There was only one cutaneous lesion, immediately above the notch of the sternum, a ragged opening leading down into the chest farther than I could determine at any time prior to the autopsy. She would come into the office, go to the washstand, lean over as far as she could and allow about a pint of turbid serum to flow out.

There was extensive involvement of the mediastinum. I am strongly inclined to believe that in most patients with Hodgkin's disease presenting enormous masses at the sides of the neck, such masses are of mediastinal origin and that what one sees are simply outgrowths from an original mediastinal mass.

I used roentgen rays without any improvement whatsoever. After some months I was summoned at night to her home in a distant part of the city. By the time I arrived the woman was sitting up in a chair dead. The floor and everything about was covered with blood. There had suddenly been a tremendous gush of blood.

At necropsy a huge mediastinal mass was found, and there and elsewhere in the tissue were a great many Sternberg-Reed cells and eosinophils.

DR SAMUEL E SWEITZER. I wish to thank Dr Senear and the members for this fine discussion. To Dr Keim I would say that we assume this to be a neoplastic disease, and we really think, as I said in the paper, that it is a form of large cell lymphosarcoma, at least the diseases are so close together that one cannot tell them apart.

In answer to Dr Peck. Our technic does not work so well in the hard tissue of the skin as it does in the soft tissue of the nodes.

I was pleased to hear Dr Osborne's remarks about the surgical removal of the lesions, if they can be found early enough, before they are disseminated.

## EXPERIMENTAL PROPHYLAXIS OF CHANCROID

FRANK C COMBES, M.D., AND ORLANDO CANIZARES, M.D.  
NEW YORK

Wars conducted on foreign soils, particularly in tropical climates, are invariably provocative of new diseases or of an increase in prevalence of those which normally occur only sporadically. Chancroid is one of the diseases belonging to the latter group, its prevention and treatment present many military, public health and economic problems. Although it is seldom observed in large urban centers of the temperate zone or in small country towns, it is particularly prevalent in the southern states, in North Africa and in the Southwest Pacific. Greenblatt appropriately described it epidemiologically as "a disease of the unclean, of the people who do not use soap and water with any degree of frequency, particularly when coitus is performed on the run."

In the armed forces stationed in the United States chancroid comprises about 6 per cent of all genitoinfectious diseases. However, in the Navy and Marine Corps, a large percentage of whose personnel serve at tropical stations, its incidence, even in peacetime (1929), mounts as high as 3 per cent of all admissions to the hospital. Its prevalence in wartime in tropical and subtropical zones in both the British and the American Armies far exceed that of syphilis.

The problem of prophylaxis was one of the first to require the attention of the Committee on Venereal Diseases of the National Research Council. Consequently, a subcommittee on the minor venereal diseases was appointed for the purpose of pursuing studies independently at the University of Georgia and New York University, of testing the efficacy of the usual prophylactic agents recommended by the Army and Navy and, subsequently, of assaying the value of other newly synthesized chemicals.

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 20, 1944.

From the Department of Dermatology and Syphilology, New York University College of Medicine, and the Third Medical Division (New York University), Bellevue Hospital.

This investigation was conducted under a grant provided by the Committee on Medical Research of the Office of Scientific Research and Development. Permission for its publication has been granted.

The report of the first phase of this investigation has been published and may be summarized as follows:

1 Soap and water, ointment of mild mercurous chloride U S P (30 per cent), mild mercurial ointment U S P, silver picrate, mild protein silver and other topical agents used for the routine prophylaxis of syphilis and gonorrhea are of little value in the prevention of chancroid.

2 Sulfanilamide powder is ineffective.

3 Sulfathiazole (10 per cent) in an ointment base (yellow ointment, U S P XII) affords protection in 80 per cent of patients if applied within one hour of exposure.

The purpose of this paper is to report on the prophylactic action against chancroid of various arsenical preparations, sulfonamide compounds and surface-active or wetting agents.

### EXPERIMENTAL STUDIES

*Method.* In the first phase of our investigation we employed the method of autoinoculation by multiple puncture, as suggested by Ravaut. This was eminently satisfactory. Besides convenience, it had the added advantage that the inoculum more closely resembled in virulence the normal infective material. There were, however, two disadvantages of this method. First, the relatively small number of patients with chancroid naturally limited the number of autoinoculations which could be made (we could not routinely make more than two at one time from a single ulcer), second, there was the possibility that in a small number of patients the inoculum, although containing *Haemophilus ducreyi*, would fail to produce the disease.

In the phase of research herein reported, cultures of *H. ducreyi* were used exclusively. The first problem was to determine the dilution of culture necessary to produce consistently a chancroidal ulcer which would not cause too intense a reaction, which would be regular in size and which would respond promptly to internal treatment with sulfathiazole. For this purpose thirty inoculations were made, with dilutions of 1:25, 1:50, 1:100 and 1:200. These were prepared with broth. The best results were obtained with a 1:25 dilution. However, the virulence of the

cultures could change rapidly, and a dilution of 1:25 might at times be as virulent as one of 1:5.

Attempts were made to count the number of organisms, with the Wright method. After some difficulty, because of the tendency of the cultured bacilli to clump and occur in chains, it was found that a 1:25 dilution contained approximately 3,000,000 organisms per cubic centimeter.

The most satisfactory stain proved to be as follows:

	Gm or Cc
Methyl green (50%)	1.00
Pyronin C C <sup>1</sup>	0.25
Alcohol (95%)	5.00
Glycerin	20.00
Phenol solution to make (2%)	100.00

The alcohol is added to the phenol solution. Then the dyes and, finally, the glycerin are added.

The stain should stand for a few weeks before it is satisfactory for use. We usually used positive smears of gonococci to check on the proper time and color. The staining time is about five minutes.

If the stain required more red, we added a little of the following stock solution:

	Gm or Cc
Pyronin	0.4
Alcohol (95%)	2.5
Glycerin	20.0
Distilled water, to make	100.0

If more green was needed, we used the same vehicle, substituting methyl green for the pyronin. After a few weeks the stain remains stable indefinitely.

All inoculations were made on the anterior surface of the thigh, without previous cleansing of the skin. The culture used had been incubated for forty-eight hours and kept in the ice box for twenty-four hours. The epidermis was cross hatched, each excoriation being 1 cm in length and of sufficient depth just to avoid bleeding.

Thirty-five inoculations were made experimentally by rubbing the virulent material into the skin for one minute without scarification. In all but 1 instance this procedure failed to induce chancroid, proving that a break in the integument is essential.

With a tuberculin syringe and a 26 gage needle, 0.01 cc of culture was placed on the scarified area and rubbed in for one minute. Four such areas on each thigh were made and then covered with sterile gauze. Prophylactic

1 C C indicates "Commission Certified" (by the Commission on Biological Stains). Because pyronin C C is no longer available, we are now using pyronin G, which is satisfactory but not as good as pyronin C C.

agents were rubbed in for one minute, with a sterile finger cot, one, three and six hours after inoculation. Clinical and bacteriologic examinations were made in forty-eight hours and on the third, fourth and fifth days.

The prophylactic agents tested included a number of arsenical preparations synthesized by the United States Public Health Service for this investigation, sulfathiazole ointment (5 and 20 per cent),<sup>2</sup> sulfanilamide ointment (5 and 10 per cent),<sup>2</sup> an ointment containing microcrystals of sulfathiazole,<sup>3</sup> and four surface-active agents, including phemerol chloride, zephiran chloride, cetylpyr (cetyl pyridinium chloride) and igepon A (sulfonated ethyl ester of oleic acid).

**Results**—The period of incubation of these artificially induced chancroids varied from two to four days. About the second day several small pustules were noticed along the cross-hatched epidermis, surrounded by a slightly edematous, erythematous halo. They were not broken. In another day or so they coalesced to form a larger, tense pustule. This was broken, and a deep ulcer, approximately 1 cm in diameter, with soft, undermined edges and filled with thick creamy pus, rich in *H. ducreyi*, was exposed.

#### LYOPHILIZATION

The strains of *H. ducreyi* in our possession, besides two isolated from patients at the Bellevue Hospital, included one from the Lederle Laboratories, Inc., which was isolated a few years ago, one from Dr. E. S. Sanderson, of the University of Georgia School of Medicine, which was isolated by Dr. Anna Dulaney, of the University of Tennessee College of Medicine, in the spring of 1942, and one isolated in May

2 The base of this ointment had the following formula:

	Gm or Cc
Stearic acid	7.60
Liquid petrolatum	3.16
Wool fat	1.26
Cetyl alcohol	0.63
Propylene glycol	10.00
Aminoacetic acid	0.65
Boric acid	0.30
Urea peroxide	0.50
Urea	0.50
Distilled water, to make	100.00

3 This ointment had the following composition:

	Gm or Cc
Spermaceti	3.00
White wax	0.40
Glyceryl monostearate	6.00
Propylene glycol	35.00
Duponol C (an alkyl sulfate)	1.00
Mild mercurous chloride	30.00
Microcrystals of sulfathiazole	15.00
Special perfume oil	0.01
Distilled water to make	100.00



1943 by Dr G W Rake and Dr W B Dunham, of the Squibb Institute. All of these strains were lyophilized. The method used was identical with that ordinarily employed for the preservation of bacteria and serums. Whole blood (rabbit), in which the organisms are routinely grown by us, was used. Cultures were prepared by adding 0.2 cc of an eighteen hour culture to pyrex tubes measuring 0.7 cm (inside diameter) by 13 cm. These were rapidly frozen by immersion in an alcohol-solid carbon dioxide mixture at a temperature of approximately 70 C, they were then dried overnight in the Mudd apparatus. The tubes were sealed and stored at room temperature.

Four weeks after lyophilization the cultures were tested for viability and virulence. They compared uniformly favorably with cultures maintained in the usual way.

#### SUMMARY AND CONCLUSIONS

Lyophilized cultures of *H. ducreyi* compare favorably with rabbit blood cultures in rate of propagation and virulence.

Contiguity of the virulent material with the epidermis is a prerequisite for infection.

The results of application of the following solutions were noted:

A 10 per cent solution of zephiran chloride in water and a 2 per cent solution in propylene glycol afforded 100 per cent protection if applied within one hour of inoculation.

A 2 per cent aqueous solution of zephiran chloride was effective in 70 per cent of cases if applied within three hours of inoculation and in 81 per cent of cases if applied within one hour. In a concentration of less than 2 per cent the degree of protection was too low to be of practical value.

A combination of mild mercurous chloride U. S. P., 30 per cent, and sulfathiazole, 15 per cent in an oil in water emulsion ointment base gave effective prophylaxis when applied in 85 per cent of cases six hours after inoculation. This is now being used experimentally in the armed forces.

All arsenical preparations and surface-active agents with the exception of zephiran chloride were unsatisfactory.

#### ABSTRACT OF DISCUSSION

Dr HAROLD N. COLF, Cleveland. The extensive experiments of Dr Combes and Dr Canizares on the prophylaxis of chancroid have been time consuming, painstaking and carefully controlled, moreover, the results are of real value.

Some time ago I was asked by the National Research Council to give my opinion as to a satisfactory com-

bined prophylactic agent against syphilitic and chancroidal infection.

I suggested that perhaps a combination of mild mercurous chloride and one of the sulfonamide drugs would answer the question, but I did not know about the possibility of incompatibility and suggested that a pharmacologist investigate it. No doubt others have made the same suggestion.

It is gratifying that the investigators found mild mercurous chloride, 30 per cent, and sulfathiazole, 15 per cent, in an oil in water emulsion to give effective prophylaxis in 85 per cent of cases six hours after inoculation.

It is also worthy of note that zephiran chloride in a 5 to 10 per cent solution also gave effective prophylaxis in a high percentage of cases. Probably this solution would be too strong to be used on the human genitalia.

The results of Dr Combes and Dr Canizares are no doubt already being widely applied in the armed forces, and they are to be congratulated on this work.

In the last year or so, the effect of repeated applications of a sulfonamide preparation to any area on the human skin has been questioned. Whether this will bring up another problem in the use of sulfonamide compounds for prophylaxis remains to be seen.

Dr LOREN W. SHAFFER, Detroit. I and other members have been much interested in the question of chemical prophylaxis as a part of the activities of the Venereal Disease Control Committee of the Michigan State Medical Society and have investigated such prophylaxis, although never with the intensity and thoroughness with which this investigation has been carried out.

Only when one undertakes a study of this field of prevention can the tremendous value of this type of work be appreciated. There has been no change in chemical prophylaxis in the past thirty years yet many new drugs are now available.

I was rather surprised that sulfonamide drugs were not more effective in this experimental work in the prevention of chancroid, since sulfonamide compounds, sulfathiazole particularly, are effective in the treatment of this disease. One would expect them to be even more effective in prophylaxis.

I should like to know whether the authors are in a position to make any statements about the experimental work that was carried out with the arsenical drugs. Since these compounds, particularly stable preparations like the arsenoxide compounds, have been experimentally demonstrated to kill treponemes in vitro in a dilution of 1:4,700,000, they should be more effective than the authors' studies have shown and should be stable enough to use locally in prophylaxis.

I should also like to know, on the basis of the experimental work, whether the investigators have any impressions about the immunity against chancroid, whether certain persons, even when they are all men, have a much higher degree of immunity against infection than others and, particularly, whether women have a higher degree of immunity than men.

It has been my impression that examination of women rarely reveals any clinical evidence of chancroidal infection. I suspect, and I believe it has been previously stated, that even in the absence of clinical manifestations women can act as carriers.

Dr E. WILLIAM ABRAMOWITZ, New York. Dr Combes and Dr Canizares have made an excellent presentation. I recall an experience I had many years ago with a preparation supposedly of bichloride of mercury, which the Metz Laboratories put out.

Bichloridol had been used for years, until the Council of Pharmacy and Chemistry of the American Medical Association tested the contents of the "plastule"—I



think they called it—and found an almost complete absence of mercury bichloride in the material

I think that every time a new product is put out, especially for a highly important purpose, some investigation should be made of its active ingredients

I also suggest that after a preparation has been placed in containers, especially containers made of various plastic materials or some other new product, it be examined at various intervals after it is released for use

DR FRANK C COMBES, New York The problem of prevention of venereal disease is somewhat more complicated than it might appear on the surface. Of course, the object of the Committee on Venereal Diseases was to find one substance which would protect against gonorrhea, syphilis, chancroid and possibly lymphogranuloma venereum

The arsenical compounds tested were in no instance more than 50 per cent effective, even when dissolved in propylene glycol. Some of them were devoid of any prophylactic value

I am opposed to the local and internal use of sulfonamide compounds for prophylaxis because of the well known danger of sensitization of tissue

In reply to the question regarding the rarity of chancroid in women, I feel that the female carrier is common and that many men contract the disease from this source, even in the absence of chancroid in the vagina or on the vulva. Dr F Mortara, of New York University, is now conducting research along these lines, and he and I have so far been partially successful in verifying this supposition, having been able to isolate viable and virulent *H. ducreyi* from the intact, apparently healthy, vaginal mucosa

Incidentally, Dr Canizares used penicillin in treating several patients who had chancroid as the result of artificial inoculation. It was remarkable how quickly the lesions became worse. Of course, the explanation is that the growth of contaminating organisms, particularly the staphylococcus, was restrained by the penicillin and that their inhibitive action on the proliferation of *H. ducreyi* was thus removed. We know that in making autoinoculations the contaminants, especially the staphylococci, will overgrow the *H. ducreyi*. By giving penicillin to some of these patients we have been able to remove these contaminants and recover almost pure smears of *H. ducreyi*.

104 East Fortieth Street

# TREATMENT OF DERMATITIS HERPETIFORMIS WITH PENICILLIN

LIEUTENANT COMMANDER C C CARPENTER (MC), USNR

AND

LIEUTENANT (JG) W H HALL JR (MC), USN

There is sufficient evidence at the present time to justify one in considering dermatitis herpetiformis a disease caused by hypersensitivity to bacteria or their products. This belief has been furthered by the reports of the rapid involution of the cutaneous lesions and the decrease in the pruritus during the continued administration of small amounts of sulfonamide compounds<sup>1</sup>. The recent investigations by Bernhardt<sup>2</sup> and others have demonstrated a cutaneous hyperreactivity to many types of bacterial extracts—namely staphylococcus and streptococcus vaccines, tuberculin and trichophyton. In some instances, as shown by Schwartz,<sup>3b</sup> the intradermal injection of autogenous colon bacillus vaccine will produce grouped papulovesicular reactions, resembling in form the early lesions of this disease. Additional evidence is found in the success of Callaway<sup>3</sup> in keeping a patient with chronic bronchitis free of this cutaneous disease while administering autogenous pneumococcus vaccine and the rapid return of the lesions when the therapy was discontinued. Pack<sup>4</sup> found that vaccine desensitization was of benefit, but he combined his administration of staphylococcus toxoid with the oral administration of thyroid.

It was therefore assumed that administration of penicillin should be rapidly beneficial to the patients with dermatitis herpetiformis but might in addition have a more lasting effect than the

therapy which has already been described. Though this disease is considered to be uncommon, we were fortunate in having available for study 6 men with typical disease who had been admitted to the hospital during the past summer months. For all but 2 of these the diagnosis had been previously made at other hospitals.

## SUMMARY OF CASES

The naval personnel who received this treatment were between the ages of 20 and 32 years. The duration of their disease varied from one month to four years. They had previously received sulfapyridine therapy, which had been of great benefit to all. The clinical distribution of the grouped papulovesicular lesions of all but 1 patient was characteristic of this disease; this man had recently returned from the South Pacific, with a pustular exacerbation. None had bullae. Some minor active foci of infection were found in 4 of the patients.

Routine laboratory data, including results of a urinalysis and a complete blood count, were normal. All Kahn reactions of the blood were negative. Only 1 patient showed a reversal of the albumin-globulin ratio. Intradermal tests with several bacterial vaccines indicated a general hyperreactivity to all tests for the entire group.

Our method of treatment was the intramuscular injection of 15,000 units of sodium penicillin every three hours. It was noted that in all patients the pruritus disappeared within the first seven injections. There was a resolution of the infiltrated erythematous base, and vesiculation disappeared, leaving a flat slightly scaly area. However, new lesions appeared at the sites of old ones as well as at previously unaffected sites within one to ten days. In the patient with the pustular eruption new grouped vesicular lesions developed after the twenty-sixth injection of penicillin and while therapy was still in progress. New pustular lesions recurred in ten weeks.

## COMMENT

The rapid improvement in all our patients while receiving injections of penicillin substantiates

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be construed as reflecting the policies of the Navy Department.

1 (a) Lam, E S, and Lamb, J H. Treatment of Pemphigoid Eruption with Sulfanilamide, *Arch Dermat & Syph* **37** 840 (May) 1938. (b) Schwartz, J H, and Lever, W F. Dermatitis Herpetiformis (Immunologic and Therapeutic Considerations), *ibid* **47** 680 (May) 1943.

2 Bernhardt, R. Weitere Beitrage zur Aetiologie des Pemphigus und der Duhringschen Krankheit, *Arch f Dermat u Syph* **171** 536, 1935.

3 Callaway, J L, and Sternberg, T H. Bacterial Allergy. An Etiologic Factor in Dermatitis Herpetiformis, *Arch Dermat & Syph* **43** 956 (June) 1941.

4 Peck, S M, in discussion on papers of Sayer and Kampf, *Arch Dermat & Syph* **38** 673 (Oct) 1938.

the theory that this disease is a form of bacterial allergy rather than a disease of neurogenic, metabolic or toxic origin. However, the effects of penicillin, like those of the sulfonamide compounds, continued only during the actual administration of the drug, and lesions soon recurred when the injections were stopped. Apparently the effectiveness of penicillin does not depend on the relative size of the total dose, as no greater improvement was noted after 1,000,000 units than after 300,000 units.

Schwartz,<sup>1b</sup> in his studies, noticed a tendency to formation of grouped papulovesicular reactions similar to the original lesions of dermatitis herpetiformis following the intradermal injections of autogenous colon bacillus vaccines. We noticed the same phenomenon with regard to both the colon bacillus vaccine and the mixed bacterial vaccines used in subsequent treatment. However vesiculation was not obtained by the intradermal injection if the patient was receiving

therapy with penicillin.<sup>5</sup> Penicillin ointments locally were not found superior to ointments made with sulfathiazole in the rapidity with which they healed early grouped lesions.

#### SUMMARY

Penicillin therapy was of immediate value in the treatment of 6 patients with dermatitis herpetiformis. However, new lesions reappeared within hours to days of its discontinuance. No more benefit was derived from the use of 1,000,000 units than from 300,000, and we believe that 300,000 units is the optimum dose.

Diagnostic intradermal tests to determine the degree of bacterial sensitivity should not be performed during the treatment with penicillin, as the patient's reactivity to the vaccine is greatly lessened at this time.

5 Roxburgh, I. A., Christie, R. V., and Roxburgh, A. C. Penicillin in the Treatment of Certain Diseases of the Skin, *Brit M J* 1:524 (April 15) 1944.

# ULCERATIVE DIPHThERIA OF THE SKIN, DESERT SORE AND TROPICAL ULCER

REPORT OF AN EPIDEMIC OBSERVED IN HAIFA, PALESTINE

S GILL, MD  
HAIFA, PALESTINE

For the third year in succession a small epidemic of ulcerative diphtheria of the skin simultaneously with desert sore was observed among the civilian population in Haifa with the beginning of the hot, damp season

This year an epidemic of tropical ulcer brought a new variant to the already seasonal bacterial ulcerations of the skin. During September 1944 I observed in the Hadassah Polyclinic 15 cases of ulcerative diphtheria, 35 cases of desert sore and 17 cases of elevated tropical ulcer. In the same month dozens of tropical ulcers were observed in other medical stations in Haifa. There is nothing exceptional in the sporadic or even in the epidemic occurrence of tropical ulcers in Palestine, but an epidemic with diphtheritic ulcers and desert sore has, to my knowledge, not been observed previously

## DIPHThERITIC ULCERS

Two forms of diphtheritic ulcers could be differentiated in their very beginning, during the first week of infection

1 *Pseudomembranous Type* There was a particular pustular lesion which resembled a ripe open seed shell. The epidermis became necrotic, and the skin was transformed into a pseudomembrane, sometimes as white as gypsum. The pseudomembrane separated from the subcutis piece by piece, leaving behind a typical punched-out ulcer or an ulcer with rolled edges

2 *Proliferating Type* In the proliferating type, after the rupture and disappearance of the pustule there was no sign of a pseudomembrane but there was observed a tender tissue quickly proliferating with a deep cavity in the middle of it. Separation of the proliferative tissue did not occur piece by piece but came about by a process of liquefying and gradual throwing off

## PARONYCHIA DIPHThERICA

Paronychia diphtherica deserves special mention because of its higher toxicity, due probably

to the anatomic structure of the finger. For the patient I treated hospitalization and repeated injections of diphtheria antitoxin were necessary

## DESERT SORE

The ulcers of desert sore did not differ from those observed in the years 1942-1943<sup>1</sup>

## TROPICAL ULCER<sup>2</sup>

In the beginning stage of tropical ulcer there was a bulla with a seropurulent and sanguino-



Fig 1—Ulcerative diphtheria of the skin of seven days' duration in a boy aged 12 years, liquefaction of the proliferated tissue and easy bleeding

1 Gill, S. Ulcerative Diphtheria of the Skin, Arch Dermat & Syph 49 408 (June) 1944

2 Ulcus Tropicum, in Manson-Bahr, P H. Mansons Tropical Diseases, London, Cassell & Co, Ltd, 1941. Ulcus Tropicum, in Strong, R P. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases, London, H K Lewis & Co, Ltd, 1942

lent content and a painful peripustular inflammation. After the rupture of the bulla a characteristic ulcer developed rapidly. A dense moist slough of yellowish color rose 0.5 to 1.5 cm above the surrounding tissues. Sometimes the slough overgrew the width of the ulcer and formed a pendulant mass on a large base. In the process of healing the slough liquefied and gradually fell off, starting always from the periphery.



Fig 2—Paronychia diphtherica of two weeks' duration in a girl aged 11 years

In some cases the periulcerative inflammation, pain, fever and constitutional disturbances were rather severe during the first week of the illness. Generally tropical ulcer tends to cause deep destruction, but in this epidemic I did not see any destruction deeper than of superficial fascia.

The size of the largest ulcer was 7 by 7 cm. One ulcer was located on the arm, all others

were on the legs. In 2 cases there were multiple ulcers.

The bacteriologic finding was invariably the same: a great amount of fusiform bacilli with no spirilla present. The elevated nature of the ulcers could explain this fact. As known from the microscopic examinations of tropical ulcers, spirilla are seldom observed in the higher zone of the ulcers. Costa recently found spirilla only in the deep zone of the ulcer.<sup>3</sup>

Treatment with sulfanilamide powder locally and covering the slough with plaster were satis-



Fig 3—Ulcus tropicum elevatum of three weeks' duration in a woman aged 40 years, clearing of the ulcer from the periphery after ten days' treatment with sulfanilamide powder

factory. The ulcers cleared in one to three weeks. In cases of severe ulcer sulfanilamide given additionally in tablets or suppositories proved helpful.

All patients treated in this epidemic were ambulatory.

36 Herzl Street

3 Costa, O. G. Tropical Ulcer, Arch Dermat & Syph 49:260 (April) 1944

# PSYCHOSOMATIC STUDIES IN DERMATOLOGY

## A THE MOTIVATION OF SELF-INDUCED ERUPTIONS

HENRY E MICHELSON, M D

MINNEAPOLIS

The knowledge of dermatoses has been largely based on morphologic descriptions and on the bacteriologic and pathologic changes involved. Since the functions of the skin are varied and do not in localized diseases necessarily affect the patient's physiologic processes to any great extent, the skin has been treated more as an autonomous organ than as an integral part of a person.

In order to comprehend diseases not as isolated dysfunctions and to find underlying causes and far reaching effects of disturbances, tremendous steps have been taken to correlate the psychic and the somatic aspects of the function of the organism. Dermatologists are in an especially advantageous position for making such observations and may offer great aid in disclosing interesting and obscure connections. If they wish to become interested in this approach to certain problems, they must endeavor to understand the person, his environment, his experiences, his adjustments and his capabilities to withstand not only the physical but the psychic trauma associated with or induced by the disease problem at hand.

Those disturbances of the skin which have their origin in the higher brain centers, operating through the autonomic nervous system, are mentioned only to call attention to their challenging complexity. The influence which the emotions have on function of the skin is illustrated by alterations in the mechanism of perspiration, as in fear, the blanching of the skin in anger, the production of "goose pimples" and the like. All these changes may occur under ordinary conditions, in special or pathologic circumstances it is self evident that they may be much aggravated. Such alterations may occur after actual damage in the so-called centers of the brain, as for example postencephalitic cutaneous changes.

Some work, but assuredly not enough, has been done to show the effects that vagus and sympa-

thetic actions have on certain dermatologic diseases. Certainly such diseases as urticaria and atopic eczema offer an excellent field for such study. The close relation between the autonomic nervous system and internal secretions as well as the control that the cerebral cortex has over these systems has been demonstrated so often that the reciprocal action between the psychic and the somatic can be accurately predicted, and it can be stated that certain psychic stimuli bring about somatic reactions with great regularity. First, it must be emphasized that not every functional change produced by the nervous system is necessarily psychic and that acute divergence in the functioning of an organ produced by psychic influences which do not bring about a fixed change is not yet a neurosis. It is only when the behavior is on a wilful or compulsion basis which regularly produces certain effects that a neurosis results. There undoubtedly is a close relationship between the psyche and the soma in that group of skin diseases called functional neuroses. In this group fall the self-induced eruptions which have long been recognized but which still leave much room for speculation as to the clear relationship between the eruption and its causes.

Dermatologists are well acquainted with the fear neuroses, exemplified by fears of sweating, of blushing, of body odor, of parasites and of hypertrichosis. The type of neurosis which causes tearing out of the hairs (occasionally the nails), including trichotillomania, as well as peeling of the skin about the nails or palms is also rather often seen. The fear of parasites which causes the patient to excoriate the skin, display bits of tissue and demand identification of the invader is a form of obsession. As is true of many patients with neurotic or psychotic diseases, a certain organ is often used to sublimate the symptoms. The effect of psychic influences on the exacerbations and course of such diseases as psoriasis, acne, lichen planus and dermatitis herpetiformis is well known. These diseases should not, however, be identified with the afore-

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Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc, Chicago, June 20, 1944



mentioned group because of their constitutional character

True psychogenic dermatoses are functional neuroses which are largely characterized by vasomotor changes, such as severe or vicarious blushing and certain forms of urticaria. *Verruca vulgaris* and *herpes simplex* may be diseases in which psychic influences favor or precipitate virus infections

Psychogenic pruritus, in particular the anal and genital forms, often is attributed to various psychic traumas, but in these instances the connection is not clear and a preconceived association may lead one far astray. A case in point is that of a woman whose marital life was unsatisfactory and who was treated for a psychogenic vulval pruritus, only at a later date to have *trichomonas vaginalis* demonstrated by a gynecologist. Cure of the itching was promptly effected on institution of appropriate local treatment

From these introductory remarks it will readily be seen that dermatology and psychiatry have a common problem in solving the causation, pathogenesis and treatment of a large number of diseases. I have felt that a sounder approach to the problem may be made if one studies diseases the morphologic characteristics of which are exact enough that a dermatologic diagnosis may be made with a high degree of certainty. The self-induced eruptions offer a good beginning, and accordingly I have attempted to search for a motive in a number of such patients

Neurotic excoriations, under various names, have been known for many years. MacKee and Pusey and Senear offered papers on the subject in 1920. They emphasized that patients who presented rather easily recognized lesions, called neurotic excoriations, readily admit the fact that they produced the lesions themselves and that they did so because of uncontrollable desires to excoriate. The authors did not, however, make an effort to ascertain why their patients chose to display their emotions or impulses on the skin

In my opinion there are two distinct types of neurotic excoriations. The first I call physical. In this group fall those patients who usually have had a preexisting cutaneous disease, most often acne or sycosis, and who really believe that they assist the cure by removing the lesions with the finger nails or with tweezers. The process becomes a ritual which female patients perform in their evening toilet and male patients in shaving. Neither the apparent cause nor the habit disturbs the patient a great deal psychically, and only if persisted in to the point of cosmetic

damage does the habit have deeper significance. It is not always easy to cure such a patient but a certain persuasive psychotherapy coupled with local treatment of the underlying dermatosis often brings about a gradual cessation of the habit. To be sure, it is impossible to call such eruptions a response to a purely physical stimulus but it must be emphasized that there is no deep-seated motive, and the reason for excoriating is well understood by the patient and easily elicited by the physician. The mild neurotic excoriations of a large number of patients belong in this group

The second type of neurotic excoriation is based on a deep-seated emotional cause, and although the patients do not necessarily attempt to deceive the examiner, nevertheless they attempt to mislead him and are in fact unable to state the real reason because of their ignorance of the mechanism of their neurosis. The difference between this type of neurotic excoriation and the so-called dermatitis autophytica or factitia is only one of degree. It is extremely difficult to list the characteristics of the persons with excoriations of the second type, they do not even have traits in common which readily may be recognized. Whereas patients with the first type are usually in the second and third decades patients with the latter type often are in the fourth or fifth decade. The history will often reveal that they have been producing lesions for years, that there is no regularity in the process, as in the first group, and that severe spells of excoriating are interspersed with periods of comparative freedom. The regions excoriated are not confined to areas frequently invaded by a known disease such as acne or sycosis but are much more likely to be the forehead, the neck, the shoulder regions, the chest and the extremities. Episodes of excoriation may be confined to local areas, so that fresh lesions may be present only in one region and older, crusted lesions and scars in others. These patients rarely excoriate before a mirror, for they do not attempt to remove a lesion, and they often excoriate at night in the dark after retiring

One must realize that excoriating the skin to the point of actual damage must provoke considerable pain and distress and the purpose and compulsion must be powerful. The importance of inhibited, repressed internally directed rage and resentment becomes very clear in some of the case histories which follow. Dr Karl Menninger has brought this out in his book entitled "Man Against Himself," and it should be read by persons interested in the subject

## CLINICAL EXAMPLES

CASE 1—*Neurotic excoriations with a previous diagnosis of scabies*

A college student, aged 19, had spent the summer in Mexico City, and a generalized itching developed on her return to college. She was told that it was due to itch mites or fleas. She was treated over a period of three months, but the eruption was periodically worse. Examination revealed various types of excoriations over the entire trunk, the chest, and also on the arms, but there was no evidence of infestation. After a few days' observation and the use of a phenolated lotion there was no improvement. Conversation with her revealed that she was the daughter of an unsuccessful attorney and that early in life she resented the family's poor economic and social position. She became shy and morose. The family moved to a small city, where their position became much improved, and from then until she entered college she was happy and contented. She went to Mexico City for the summer, procured a position in an embassy and wished to remain there, but her family insisted on her return. As soon as she reentered college she became depressed, felt her financial limitation and was dissatisfied with her lot. She began to excoriate her skin, wishing to appear too uncomfortable to remain in college. On one occasion when shopping for a party gown, she saw one that she liked, but, as she could not afford it, she was thrown into a rage which she relieved by excoriating.

When the facts were evaluated and explained to her, she said that she had always been a "picker" and realized that the excoriating was an external sign of her resentment and suppressed anger. She was very ambitious and felt that she had always been thwarted by her family, her father in particular, this feeling dated back to his early failure and was again a source of annoyance when he insisted on her return to college. When it was pointed out that if she wished a career it would be open to her after graduation, she agreed to return to college, where she gradually adjusted herself and ceased excoriating.

CASE 2—*Hypertrichosis with excoriations*

The patient, aged 49, married and the mother of one child, consulted an internist because she was extremely tired and was much annoyed by a rather recent growth of hair on her face. Because she had a lowered basal metabolic rate, the internist thought that her condition could be explained on an endocrine basis, and she was referred to me for treatment of the hypertrichosis.

Examination revealed a degree of hair growth which was well within the limits of normal for her age. Questioning revealed that her symptoms were decidedly those of a severe depression. I referred her to Dr. Roy R. Grinker, of Chicago. Excerpts from his report follow:

"Mrs. W. presents a classic example of involutional melancholia with agitation and obsessions. Her life has been filled with minor depressions occasioned by hypersensitivity. She is a perfectionist. Behind all this is a severe repression of a strong attachment to the father, renounced and reacted against. Her conscious attitude is one of being an average person and of deserving little. In unconscious protest, she married a man who represents the opposite of the father.

"At the onset of her difficulty it seemed as if preoccupation with hairs on the chin was the total problem, but it was followed by insomnia, loss of appetite, loss of weight, agitation, loss of interest and attention and ideas of suicide. This full-blown melancholia was projected onto the face. At the same time, the menstrual

flow decreased in intensity and hot flashes and dizzy spells occurred. Thus there is a distinct relationship in this case between onset of severe depression and menopausal symptoms.

"The patient has no insight and insists that the depression is a result of hair growth. I believe that I was able to assure her of the absence of insanity and of the good prognosis for recovery. She will get well, and she already has made good progress toward that end. Her depression has already lifted considerably, and in the next few months one should see considerable improvement.

"I cannot give her psychologic insight—her ego is not mature enough—and to touch now on her neurotic attachments would be exceedingly unwise." In addition to endocrine treatment, use of placebos was advised.

It will be noted that, as is often the case, the patient's condition had at first been explained entirely on an endocrine basis. I treated her with the help of Dr. Grinker. My so-called psychic depilation was done with an occasional irradiation and bland ointments. She gradually improved, ceased excoriating and finally became entirely well. It must be admitted, however, that she was under treatment for two and one-half years.

CASE 3—*Persistent excoriation, possibly on an erotic basis*

A farm girl, aged 16, was referred because of a severe eruption on the legs and arms. She stated that the eruption had been present for ten years. Examination revealed no underlying dermatosis. The dermatologic diagnosis was neurotic excoriations, which were freely admitted. The patient was one of five children. She stated that she slept with her only sister and excoriated in bed every night after her sister was asleep. She noticed blood on the bedclothes every morning. Very little further information could be elicited. She had completed eight grades of rural school, she said she felt that her family needed her, and so she did not continue school. She resented direct questions about her life. She said that she worked hard and had no social activities, although she occasionally attended dances but did not dance. She had no male friends but liked her brothers. When asked if she ever hoped to marry, she emphatically said "No." I could not find out whether she got pleasure from excoriating. After the third interview she bluntly stated in poor English and with much defiance that she liked to dig into her skin, did not care to be treated and did not want to stop excoriating.

My conclusion was that she should be referred to a child psychologist and her intelligence quotient, personal index, etc., ascertained. She may have been in an early psychotic condition. The excoriations may have had an erotic basis. I doubt that any treatment could cure her.

CASE 4—*Neurotic excoriations on a psychotic basis*

Mrs. X, aged 56, had been married thirty-five years and had two living children. She had had an unhappy childhood and expressed a lasting hatred of her father. She was a quiet, cultured woman, well read, much interested in flowers and possessing a sound botanic knowledge. She expressed a desire to continue her general education and stated that she felt she had advanced far beyond her husband, although she liked him and did not condemn him in any way. She had excoriated her skin for years. She did not know why and wanted an explanation. She had consulted many physicians and had been treated in various ways, but never for a nervous or mental ailment. A short interview convinced me that her troubles were deep seated,

and she was referred to Dr Roy R Grinker, whose observations follow

"Mrs X arrived, and I had her hospitalized for the purpose of getting material of a deeper psychologic nature by the use of intravenous injections of amytal. We obtained the definite evidence that her lesions were self produced, although she does not have conscious insight into the fact that the whole cutaneous picture is produced by her own manipulation. I have a lengthy history which indicates clearly that the patient is psychotic but protects herself from an actual outbreak of self excoriation and bleeding. In the first place, no one can cure this patient, but should one disturb her symptomatic defense the result will be a serious psychosis. We must therefore leave well enough alone and encourage her to find some congenial companion and go, as she desires, to Mexico and learn Spanish."

This woman's excoriating in many ways is similar to that in the previous case. It seems to be a necessary phenomenon to keep her "on an even keel." The futility of dermatologic handling is readily realized.

*CASE 5—Neurotic excoriations based on a fear of trichinosis*

A man aged 28, married seven years and the father of one child, was referred because of linear excoriations on both arms along the fossa between the biceps muscles, which had been present for five years. He had been treated by several dermatologists, without result, and was told to "forget it." The interview revealed that he was one of ten children, that he had been born on a farm and that his mother had died when he was 7. He had worked since childhood but had finished high school. Shortly after the mother's death the father moved the family to a small city. Here the boy was introduced to happy homes when he visited his companions. He developed a great resentment and would go into the attic and have long crying spells.

In all questioning regarding his wife he emphasized her kindness. Finally on the question of religion he became voluble, he said his wife was a Seventh-Day Adventist, that she had not succeeded in converting him and that she was particularly alarmed when he ate pork. She furnished him with much religious literature, and some of it contained descriptions of trichinosis. He became convinced that he was infested and could feel the worms crawling up his blood vessels, this caused the excoriating. A thorough explanation was all that was necessary, and he stopped excoriating.

*CASE 6—Neurotic excoriations with carcinophobia*

This patient, aged 43, the mother of two children, was referred because of several deeply excoriated lesions on the forehead and chin. Examination revealed many small scars about the face. She openly admitted self induction of the lesions but stated that recently she had feared the lesions were cancers. She was a woman of striking appearance but was overdressed and used cosmetics too liberally. She stated that she had been under the care of a number of physicians. Because she was so tired, she had been told that she was entering the menopause and had received estrone and injections of liver.

Interviews revealed that her husband was a busy attorney and that in recent years he had almost entirely ignored her. He worked every evening and was away from home a great deal attending court in nearby cities. She had become resigned but felt much slighted. Throughout the interview she repeated that she thought that she was attractive and that she spent much time and thought on her toilet and clothes but that her husband never noticed her. She stated that she had not associated with other men. She finally admitted that the

excoriations were purposeful and that when they caused her husband no concern she decided to try to make him believe that they were cancers. She refused to allow me to talk the matter over with her husband, saying that it would do no good. I felt that she enjoyed this feeling of being a martyr, that there was a high degree of frigidity present and that the lack of attention was really desired. An effort to point out that she should be proud of her husband's success and that she could be of great help to him met with no response.

This patient demonstrates to me that many patients excoriate because they want to hurt some one and being unable to do so, they hurt themselves and are not willing to have underlying causes discussed or eliminated. They prefer to see one physician after another, merely to be able to say that no one understands the case.

*CASE 7—Neurotic excoriations and anxiety neurosis*

Mrs McC, aged 56, came to me because of severe excoriations on the neck and arms. The history revealed repeated attacks over an extended period. The interview led me to refer her to Dr Gordon R Kammann, who reported in part:

"Shortly after Christmas 1942 the patient began to have an itching eruption on the dorsum of the right hand. This soon spread to the left hand, then formed a ring around her neck and then appeared around the eyes. The eruption came and went and was much better during the summer months, although it never completely disappeared from the hands. Last fall the dermatitis reappeared around the neck and eyes and became worse on the hands. Her one married daughter and husband and one single daughter were home on a visit for two weeks at the Christmas holidays, and during this time the skin was much better. Early in January 1944 the eruption and itching became much worse, and the condition has been variable ever since. At times it becomes red and feverish and scales, and at other times it becomes more dormant.

"The patient states that you think the condition is due to nervousness and she is inclined to agree with you, because she is 'restless.' She reads a great deal, and she finds that after she has read for a while she begins to feel ill at ease and must move to a different chair and place her reading material on a table. It does not make much difference what she reads, but she still says it is the material that bothers her at times.

"She was asked if she is worried about anything, and she said that she is 'over that period.' She then went on to say 'When your children start to marry it is the hardest time in your life. When your children marry somebody you are not interested in, it makes you unhappy. Three of my children married in one year—that was the year I had poliomyelitis—and it was all very hard on me.' The first to be married was the youngest daughter, and there was a difference in religion. The patient thinks that this is bad for both sides, although she admits that her daughter is happy. The next to be married was the second youngest daughter, and this is an agreeable marriage. The next to be married was her son, and the patient was very much opposed to this marriage, she says that the two are not mated. She is not the girl he should have married, and, at the same time, she did not get what she should have.

"I believe that there is enough in this patient's psychiatric background to produce resentment of a sufficient degree to cause her to produce neurotic excoriations. I explained to her the relationship between anxiety, restlessness and itching of the skin. I told her that one could have unconscious anxiety which could produce any one of a great variety of symptoms, including itching and even actual eruption of the skin. I then went on to explain to her how much, if not all, of her resentment revolved around the concern she has about

her daughters. It was interesting to notice how she accepted this, and after she had thought it over for a while she related an experience which she had twenty years previously. At that time her daughter was playing out of doors with some other children and wanted to play a few minutes more before coming in for supper. She consented, and in a few minutes the daughter fell and broke one of her front teeth. When the girl entered the house, the mother was much upset, and she said, 'My whole face swelled, got red and itched.' Needless to say, I used this episode to emphasize to her the intimate relationship between emotional reactions and cutaneous disorders."

CASE 8—*Neurotic excoriations and enuresis*. A 9 year old girl was sent to me because of an eruption on the buttocks. The history revealed enuresis, which had begun three years previously. It was easily noticed that the child had some purpose in excoriating the "wet areas," so I referred her to Dr. Reynold A. Jensen, a child psychiatrist, who reported that the child had many conflicts centering around the father, who drank considerably and amazed the child by his antics. The family had moved into a new district, where school difficulties were considered to be the cause of the enuresis. The excoriations began when an added load of music lessons, a whim of the mother's was added to her already existing educational difficulties. Adjustment by way of parental education was the mode of treatment advocated. I have no report from Dr. Jensen on the outcome.

#### CASE 9—*Dermatitis factitia and morphinism*

A married woman, aged 53, was referred because of large suppurating ulcers in the supraclavicular spaces. Similar ulcers were on the legs and abdominal wall. The history revealed a long series of diseases, including four "major abdominal operations," and chronic arthritis of the spine for which she had been treated. My interview with her finally resulted in a confession of self induction, and I then discovered that the secondary exploitation was to get morphine from her physician. She was referred to Dr. Hewitt B. Hannah, a psychiatrist, who reported that he did not believe it would be possible to cure this woman of her long-established habit. We believed that all her diseases and operations were based on some underlying psychogenic cause. While under our care she had a terminating cerebral hemorrhage, and necropsy revealed no demonstrable diseased organs or disease of the spine.

Drug addiction must be considered as both a cause and a result of unrecognized self-induced eruptions, because persons who are so constituted that they will produce severe lesions are very susceptible to formation of other pernicious habits, especially addiction to soporific or narcotic drugs.

#### CASE 10—*Dermatitis factitia with hysteria*

This patient, aged 44, was referred to my service at the University of Minnesota because of several large ulcers on her left breast. Similar lesions had existed on the right breast, and a partial amputation had been done by a surgeon because of the great pain experienced by the patient.

The eruption on the breast was easily diagnosed. The lesions had been produced by gouging. The patient was hospitalized and was examined by members of the psychiatric staff. No admission could be elicited. I had several long interviews with the patient and finally won her over to the extent that she agreed with me that the mutilation would not occur again, but I got no confession. I believe that this woman was not consciously aware of producing the lesions. She had attacks of great pain, swooning and loss of memory, which may have been true hysteria.

Her background gave sufficient reasons for decided psychic trauma. She was an orphan, and at 3 years of age she lived with her grandmother and aunt. The aunt married and had three children. The aunt's husband was addicted to alcohol and abused her. He died when the patient was 12 years of age. The aunt remarried and her second husband made a slave of the patient. She led a miserable life. She left home at 17 and married at 18. She was an admirable person in many respects, unusually fond of her husband and children and interested in simple but useful household arts.

The only reason I could get for her attempts to elicit pity was her statement that her husband was the only man who had been kind to her. She seemed to fear her ability to hold him, and when he left each fall to work in the harvest field the attacks occurred.

A discussion of hysterical eruptions cannot be entered into here, for it is a field in itself. However, it should be mentioned that self-induced eruptions may be produced in a hysterical manner, without conscious knowledge on the part of the patient. The motive, to be sure, is intent to deceive, but the cause is only the desire to be sick. In a case of any self-induced eruption which is not readily admitted a discovery of the means often prompts a confession, but the hysterical person who is simulating disease strives hard to uphold the fiction of a cutaneous disease otherwise acquired and tries to find ways and means for renewed deception. He tries to have "relapses" occur and to convince one of the genuineness of his sickness. These persons have the desire to be sick in order to escape the misery of their lives and their inner conflicts.

#### COMMENT

I think that I have cited enough histories to impress the fact that in many cases patients with self-induced eruptions have a background which will account for the eruption and which should be brought out if possible. The dermatologist may be able to accomplish this himself, but he must be always on the alert for serious neurotic or psychotic indications and he should refer such patients at once to psychiatrists. It will be noted that not a single neurosis or psychosis but a complex pattern of reactions underlies the excoriations. Therefore, the cutaneous eruption is no index whatsoever of the underlying condition.

I have purposely not discussed other types of eruptions which may have psychic significance. I must, however, mention occupational neuroses of the skin. Patients with them resemble to some extent at least patients who produce eruptions, for they have the desire to prolong an occupational dermatitis either by increasing subjective symptoms or by actually excoriating existing inflamed areas. They insist on the serious-

ness of their condition and the impossibility of returning to work and demand removal from all work. Then demands for prolonged compensation make them a serious problem. It must be stressed that, although some of these patients are malingerers, others are not and have rather a neurogenic or even psychogenic background. In present day industry the need for psychiatric evaluation of patients with unduly protracted diseases must be emphasized.

Some writers believe that the self-induced eruptions have been overemphasized by dermatologists because the morphologic diagnosis can readily be made and that many other cutaneous signs may be an index to underlying neuroses. This is undoubtedly true, but I believe that if one makes an effort to understand patients with self-induced lesions, one may enlarge one's positive knowledge to the point where trivial signs may be more quickly and readily diagnosed as indicative of some of the underlying neuroses or psychoses that study of self-induced eruptions revealed.

The treatment of the patient with self-induced eruptions is always an individual problem. Some dermatologists undoubtedly are able to guide patients through a period in their life when they are battling against the intrinsic and extrinsic causes of their difficulties, but no dermatologist should attempt either to treat or to aid in the treatment when there is frank mental disease present. These patients are preeminently "one doctor" patients, and even a superficial knowledge of psychotherapy teaches one that the relationship between the patient and his physician must not be upset by contrary opinions or even implied doubts or criticisms of the procedures employed. Persuasive or supportive advice is part of the therapy and, to be sure, is employed by dermatologists, but psychotherapy is a specialty and can be employed sensibly only by persons trained in the field. Psychotherapy, shock treatment and many other methods may be necessary to bring about an ultimate return to a normal life for the patient whose external sign is only a few "neurotic excoriations."



# PSYCHOSOMATIC STUDIES IN DERMATOLOGY

## B PSYCHOBIOLOGIC STUDIES OF PATIENTS WITH ATOPIC ECZEMA (DISSEMINATED NEURODERMATITIS)

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As was recently pointed out by Obermayer,<sup>1</sup> dermatologists are generally unwilling to discuss psychosomatic relationships or commit themselves to other than morphologically descriptive diagnoses of the disorders which some regard as neurodermatoses. He enumerated possible explanations for such an attitude, but it would seem that the time must have arrived when dermatologists can discuss functional disorders without reticence or apology. In other medical specialties there has been increasing interest in the so-called functional disorders and there are various estimates of their incidence. Investigators interested in psychosomatic relationships in medicine commonly estimate that one third of all patients have disorders initiated by psychic or emotional factors, another third have "physical" diseases which are gravely influenced by such factors, and the remaining third have diseases in which psychic influences are of little or no importance and the structural changes far outweigh them.

The considerable literature which relates the association between skin and nervous system has been thoroughly reviewed by Sack<sup>2</sup> and more recently by Dunbar.<sup>3</sup> It has long been noted that many cutaneous functions are subject to influence by the autonomic nervous system and that emotional disturbances influence these functions in both a qualitative and a quantitative manner (perspiration, blushing, blanching, goose flesh). Early students of psychosomatic relationships demonstrated clearly that bullae and other stig-

mas can be produced by psychic influence. The less bizarre cutaneous changes have been studied by numerous dermatologists, who attempted to classify the dermatoses subject to nervous influences. Such classifications failed to clarify the problem or stimulate dermatologic interest.<sup>4</sup> Sack<sup>5</sup> pointed out that a simple division into pruriginous and nonpruriginous diseases places in the cases of the latter group those in which the patient's personality is less likely to be influenced by the cutaneous disease. Odd and interesting cutaneous changes are produced by malingerers and hysterical persons, but such eruptions are rare. Michelson<sup>6</sup> has pointed out the variations in the dermatologic reaction and the psychic background observed in persons with other and more common forms of self-induced eruptions. In recent years a number of individual case reports (chiefly by psychiatrists) have pointed out details of psychic influences in patients with regional or general pruritus, neurotic excoriations and eczema.<sup>7</sup> Dermatologists have exhibited slight interest in such reports, partly because their educational and clinical background has been largely morphologic in its emphasis and partly because of distrust of psychoanalysts' preoccupation with sexual factors. Such reports serve to endorse the earlier knowledge, but their paucity suggests that psychic influence is rarely exerted on the skin, whereas the reverse is undoubtedly true.

4 Eller, J. J. Neurogenic and Psychogenic Disorders of the Skin, *M. J. & Rec.* **129** 481, 1929.  
Jadassohn, J. Erfolge und Grenzen der Psychotherapie bei Hautkrankheiten, *Dermat. Wchnschr.* **94** 20, 1932.

5 Sack, W. T. Zur Pathogenese und Psychotherapie der Hautkrankheiten, *Arch. f. Dermat. u. Syph.* **151** 206, 1926, *Psychotherapie und Hautkrankheiten*, *Dermat. Wchnschr.* **84** 16, 1927.

6 Michelson, H. E. The Motivation of Self-Induced Eruptions, *Arch. Dermat. & Syph.*, this issue, p. 245.

7 Cormia, F. E., and Slight, D. Psychogenic Factors in Dermatoses, *Canad. M. A. J.* **33** 527, 1935.  
Ackerman, N. W. Personality Factors in Neurodermitis—A Case Study, *Psychosom. Med.* **1** 366, 1939.  
Miller, M. L. A Psychological Study of a Case of Eczema and a Case of Neurodermatitis, *ibid.* **4** 82, 1942.

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1 Obermayer, M. E. Functional Factors in Common Dermatoses, *J. A. M. A.* **122** 862 (July 24) 1943.

2 Sack, W. T. Psyche und Haut, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin: J. Springer, 1933, vol. 4, pt. 2, p. 1370.

3 Dunbar, H. F. Emotions and Bodily Changes, New York: Columbia University Press, 1935, chap. 14.



Psychic and emotional factors in more commonly observed dermatoses have been emphasized particularly by Stokes, Becker, Obermayer and their associates<sup>8</sup>. They have called attention to the obvious fallacies of the "single cause" concept for most dermatoses and have pointed out the frequency with which "tension" can be demonstrated in association with a number of dermatologic conditions which may be spoken of as neurodermatoses. (The term "neurodermatosis" must not be confused with "neurodermatitis". Disseminated or generalized neurodermatitis is another name for atopic eczema, the cutaneous member of the eczema-asthma-hay fever complex.) Stokes and Becker have repeatedly listed the obvious clinical features by which one can usually recognize the patient with tension and have outlined relatively simple and nonspecific measures which may be prescribed to relieve tension and exert a favorable influence on many eruptions. The presence of tension does not prove a causal relationship with a patient's eruption, but the appearance and course of most cutaneous disorders are modified by the degree of the patient's tension. Relief of tension by sedation, rest and the DGAD (don't give a damn) program (Stokes) is frequently sufficient to relieve those neurodermatoses which are less severe or which have not been present too long. In case of the severe and more chronic diseases deeper investigation and more detailed study will probably lead to more effective treatment. As one advances in this field "the physician must be able to define the specific mental factors producing the illness rather than to be satisfied with vague generalizations about 'neurogenic background'." Weiss and Spurgeon<sup>9</sup> have further pointed out that one must understand the background of the patient's anxiety—whether the conflict is chiefly a product of the impact on the patient's specific emotional makeup of the present or the past external situation or, as is usually the case, of a combination of the two.

Atopic eczema takes high rank among the most chronic and generally unpleasant dermatoses,

8 (a) Stokes, J. H. The Nervous and Mental Component in Cutaneous Disease, Pennsylvania M. J. **35** 229, 1932, (b) Functional Neuroses as Complications of Organic Disease, J. A. M. A. **105** 1007 (Sept 28) 1935. (c) Stokes, J. H., and Beerman, H. Psychosomatic Correlations in Allergic Conditions, Psychosom. Med. **2** 438, 1940. (d) Stokes, J. H. Fundamentals of Medical Dermatology, Department of Dermatology Book Fund, ed 7, Philadelphia, 1942. (e) Becker, S. W., and Obermayer, M. E. Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940. (f) Obermayer<sup>1</sup>.

9 Weiss, E., and Spurgeon, O. S. Psychosomatic Medicine, Philadelphia, W. B. Saunders Company, 1943.

and severe forms are seldom effectively relieved by either the dermatologic or the allergic approach. As Stokes has indicated, in adolescents and adults the fixed and specific allergic reactions are much less important than the inborn inveterate propensity to react.

Medical practitioners have long noted an association between emotional disturbances and allergic disease, though the nature of the relationship has been vague and subject to various interpretations<sup>10</sup>. Physicians more impressed by somatic changes think that the severity and duration of the illness lead to the psychic and emotional disturbances, while others have regarded the psychic influences as of primary importance or at least as factors precipitating exacerbations of the physical changes, still others have suggested that an additional and as yet obscure factor may underlie both the psychic and the somatic pathologic processes. Among persons having the eczema-asthma-hay fever complex the nature of the emotional disturbance is not entirely clear, though several observers have pointed out general factors common to most such patients. As children they are usually said to be restless, irritable, more than normally intelligent, ambitious, hyperactive, mentally sensitive and self absorbed, and there is frequently a disturbed parent-child relationship, with overanxiety present in one or both parents and utilized by the child in developing his trend toward aggression and dominance<sup>11</sup>.

An investigation somewhat comparable with that of the present study was made by van de Erve and Becker,<sup>12</sup> who studied 79 patients with various dermatoses characterized by "neurocirculatory instability". Anthropometric measurements showed no striking abnormality, the sedimentation rate of the blood was normal, there were vascular hypotension, rapid pulse and increased sweating. The patients were physically hyperactive. Most of the eruptions were worse in the winter, and in the patients' families was a high incidence of functional disease. As a rule the patients were above normal in the intellectual characteristics (learning, memory, judgment, planning, etc.), but their success in work was

10 Sulzberger, M. B. Dermatologic Allergy, Springfield, Ill. Charles C. Thomas, Publisher, 1940 p. 170.

11 (a) Rogerson, C. H. Psychological Factors in Skin Diseases, Practitioner **142** 17, 1939. (b) Stokes, J. H., and Beerman, H.<sup>8c</sup> (c) Dunbar, F. Psychosomatic Diagnosis, New York, Paul B. Hoeber, Inc., 1943. (d) Loftus, T. A., Gold, H., and Diethelm, O. Cardiac Changes in Emotion, read at meeting of American Psychiatric Association, Philadelphia, May 1944.

12 van de Erve, J. M., and Becker, S. W. Functional Studies in Patients with the Neurodermatoses, J. A. M. A. **105** 1098 (Oct 5) 1935.

regarded as partly due to overconscientiousness. In self estimation of their emotional characteristics they rated themselves as lacking in gregariousness, self confidence and stability of moods and as above the average in excitability, consideration for others, feelings of insecurity, aggressiveness and ability to subordinate sentiment. When their patients were grouped according to the specific dermatologic diagnosis, van de Erve and Becker noted close resemblances among those with exudative neurodermatitis and dyshidrosis and among those with dry forms of neurodermatitis and pruritus ani or vulvae, but those patients with urticaria were decidedly different in many of the observed manifestations.

#### PSYCHOBIOLOGIC DEFINITION AND REFERENCE

Physiologic reactions are commonly recognized as results of such emotions as fear, anxiety, resentment, hate and anger. There is increasing evidence to support the deduction that, together with the other variable determinants, constitution and personality structure, distinct emotions produce relatively specific physiologic concomitants. Investigations of such reactions, for example, have been reported by Diethelm<sup>13</sup> on dextrose metabolism, Milhorat, Small, and Diethelm<sup>14</sup> on leukocytosis, Wolff<sup>15</sup> on gastric function, and Brown and Goitein<sup>16</sup> on asthma. The possibility that tissue changes may result from long-continued or recurring emotional states has again recently been stated by Loftus.<sup>17</sup> Two recent references have been made to an important dynamic relationship of somatic change based on emotions. Diethelm<sup>17</sup> stated that the "dynamic factor of suppression of emotion may well be present in psychosomatic conditions whereas repression (with dissociation, displacement and substitution) characterizes psychoneurotic reactions" (Similar references were made in "Orientation to Studies in Psychopathology" from the Menninger Clinic<sup>18</sup>). Suppression denotes a holding in abeyance—conscious but unexpressed or unrelieved while

repression denotes dissociation or divorce from consciousness and expression of the emotion through displacement or other psychologic mechanisms. Thus, psychosomatic symptoms might be expected at least as frequently in normal personalities as in neurotic or otherwise psychopathologic personalities, and they might then bear either a coincidental or indirect causal relationship.

#### PROCEDURE AND CLINICAL MATERIAL

Since emotional disturbance is so common and one can so easily discover evidence of tension in patients with eczema, we decided to subject to thorough psychobiologic study a group of persons with eczema. In spite of variations in individual cases, the cutaneous manifestations of atopic eczema follow such a characteristic pattern as to site, course and symptoms that it was thought the emotional and psychic manifestations might also be found to have features in common. The present report is chiefly concerned with studies and discussion of atopic eczema (disseminated neurodermatitis) as observed in persons 18 to 26 years of age (2 persons in the series were 40 and 54 years old). For none of 13 persons referred to the psychiatrist could the dermatologist have made any other diagnosis than atopic eczema (disseminated neurodermatitis). The patients were selected only in the sense that the dermatologist did not refer patients with manifestations of lesser duration or severity, in whose cases there might be more doubt as to the correct classification of the eruption. There were 3 men and 10 women. The diagnosis of atopic eczema was based on the well known clinical features of the eruption and supported by the following evidence. The eruption involved the hands in 7 instances, the face or neck in 7, the cubital and popliteal areas in 3 and the thighs and legs in 1 instance each. In 4 instances eczema appeared in infancy and persisted practically constantly. In 8 instances the eruption appeared between the ages of 10 and 18 years and followed an irregular course. In another instance it was first seen on the neck and legs of the patient at 24 years, after which it followed an irregular course for six years. Both this patient and his family presented other evidences of atopy, and the diagnosis could hardly be questioned.

Later in the study it was decided to include 4 patients (3 men and 1 woman) whose eczematous eruptions appeared later in life, at from 18 to 33 years of age, and for whom the familial and personal history of atopy was lacking or doubtful (late exudative diathesis of Rost). In most of these subjects the eruption was acute

13 Diethelm, O. Influence of Emotions on Dextrose Tolerance, *Arch Neurol & Psychiat* 36 342 (Aug) 1936

14 Milhorat, A. T., Small, S. M., and Diethelm, O. Leukocytosis During Various Emotional States, *Arch Neurol & Psychiat* 47 779 (May) 1942

15 Wolff, H. G. Emotions and Gastric Functions, *Science* 98 481, 1943

16 Brown, E. A., and Goitein, P. L. Some Aspects of Mind in Asthma and Allergy, *J Nerv & Ment Dis* 98 638, 1943

17 Diethelm, O., cited by Sladin, J. F. *Psychiatry and the War*, Springfield, Ill., Charles C. Thomas, Publisher, 1944

18 Diethelm, O. Orientation to Studies in Psychopathology, *Bull Menninger Clin* 8 65, 1944.

or recurrent and subacute, none would have been regarded as having lichen simplex chronicus, and the eruptions had been present from six months to fourteen years. The eruption was less extensive, severe or chronic than in the larger group of patients. In the patient whose disease was of longest duration only one hand was involved, in the others the hands and feet, the arms and the face, neck and hands were affected.

In all, 17 patients were studied by the psychiatrist. These persons, 11 women and 6 men, were drawn from a college student body and faculty and were informed that they were being studied for personality factors in their eruptions. Records of previous complete physical examinations (routine college entrance or health examinations) and general medical outpatient records were used. As often as was possible the following clinical and laboratory studies were performed, determination of basal metabolic rate, white blood cell count with differential studies and determinations of the sedimentation rate of the red blood cells, blood pressure (pulse pressure) and effect of exercise on the pulse rate. These procedures were chosen because of their obvious relationship with neurocirculatory instability or atopy. With 1 exception all subjects completed any requirements voluntarily and with interest and a high degree of cooperation.

Sixteen of the patients were studied by the allergist, intradermal skin tests were applied in 11 cases. Strong reactions correlated with the known facts and were therefore considered significant in 9 cases. The tests elicited negative reactions or failed to correlate with the history in 2 cases. Lack of time and the fact that these patients came under treatment by the dermatologist or the psychiatrist did not allow proper evaluation of systematic allergic management. Two of the patients were unquestionably benefited by management for allergy, while in 4 no benefit was observed in the period allowed for study of the allergy. Whether these 4 would have responded satisfactorily without dermatologic or psychiatric help is doubtful.

Personality aspects of constellation and dynamics were studied by interview technique and certain psychologic tests.<sup>19</sup> The basis of deduction was formed by such analyses, together with personal histories of chronologically parallel bodily happenings and developmental facts, psychologic and behavioral reactions and circumstantial or environmental conditions. Each case

was then evaluated as a psychobiologic entity of reaction according to the procedure of distributive analysis advanced by Adolf Meyer. Thus, constitutional and somatic factors together with personality structure, psychodynamics and situational conditions were considered. Outstanding findings and dynamics encountered were then summarized and relationships within and between the diagnostic groups noted.

Only the psychotherapeutic efforts incidental to study were used. No effort was made to evaluate psychotherapy per se, since the subjects were also subject to treatment by dermatologic and allergic techniques. Seven of them showed considerable psychotherapeutic response, 5 are continuing psychiatric treatment. Four of these also demonstrated striking cutaneous improvement, but they were included in the group responding favorably to dermatologic treatment as well. Subjects whose eruption started in infancy (4) showed no appreciable psychotherapeutic response and only 1 in the group in which it was of late occurrence did so. Topical and roentgenologic therapy was used sparingly. Phenobarbital was prescribed in several instances. Of 9 patients with atopic eczema for whom dermatologic therapy was fairly tried there was a satisfactory degree of improvement in 5, in the remainder the eruption exhibited its well recognized refractory nature. In the 3 patients with late exudative diathesis for whom dermatologic therapy was fairly tried the response was satisfactory, in contrast with the frequent failure in the other group of patients.

#### CLINICAL OBSERVATIONS

Constitutional and hereditary factors were evident by reason of the patient's atopy and the personal and familial histories of allergy. The family history of 9 patients was positive for major allergy, that of the others, including 3 of the 4 with "late" manifestations, negative or doubtful. Eight of the patients studied had other major allergic manifestations (hay fever, asthma, migraine or allergic rhinitis), 3 others gave a history of recurrent urticaria, and the remaining 5 apparently had no allergy other than atopic dermatitis. In the latter group fall all 4 of the patients with late exudative diathesis.

Twelve patients complained of fatigue. Yet all of them except 1 would have to be accounted vigorous persons, this fact again pointing to a constitutional element. Vigorousness was borne out by the appearance and observed actions as well as by the history of past accomplishment and the present load activity. The impression of vigor was heightened by the degree of alert-

<sup>19</sup> Rorschach, Bellevue-Wechsler and Minnesota Multiphasic Personality Inventory tests were administered. Various vocational aptitude and academic rating test scores were variably available.

ness and tension (psychobiologic preparedness for action) evident throughout. For the 1 exception whose vigor might be questioned there was little or no superficial evidence of tension but a decided degree of inner tension was revealed in interviews. This woman of 33, whose eruption appeared late and was limited in extent, showed the lowest basal metabolic rate (27 per cent) and the greatest overweight (128 per cent of normal) for the group. Her past and present record of activity confirmed the fact of inordinate vigor.

Physical examination revealed no gross type (there were no anthropometric studies). Examiners had classified 5 subjects as asthenic, 10 as sthenic and 2 as hypersthenic in build without apparent relation to the age of onset or character of the eruption. Body weight varied from 78 to 128 per cent of normal for height, age and sex. There were 5 patients who were 10 or more per cent above normal weight but only 2 of these could be classified as obese. All of those with late exudative diathesis were normal or above normal weight, while the atopic patients showed a decided tendency to underweight. Pulse pressures ranged from 34 to 64 mm of mercury, with an average of 38.5 mm. Determinations of pulse rates showed 1 subject with bradycardia, 5 with tachycardia and 11 with normal rates. Response to exercise as judged by pulse rate was poor in 4 cases and good or excellent in the remainder. Basal metabolic rates varied from 0 to 27 per cent. Sedimentation rates of the red blood cells were normal. The white blood cell counts tended to be low and varied from 4,450 to 8,000 per cubic millimeter.

Of the 11 subjects who had asthma or chronic rhinitis, 7 showed apparently distinctive and additional psychologic dynamics. Constitutional and heredity factors in personality were most evident from the family and personal histories of 3 persons demonstrating cyclothymic trends (cyclic variation of mood). These were found in persons whose eruption began in adolescence and who likewise had asthma. Four other asthmatic persons revealed no cyclothymic factor. In 2 patients whose eczema began in infancy there was no evidence for precipitating or modifying factors of an environmental character. This may be negative evidence for the hereditary factors. Personality factors and dynamics as found to be modified or dependent on experience or development will be considered separately.

There was found evidence for the production or modification of personality structure and dynamics compatible with the findings in each experiential history except in case of the 2

subjects mentioned in the preceding paragraph. Whether by inheritance or experience, in the case of a man whose eczema began in infancy the similarity between his personality and that of four immediate relatives (mother, maternal grandfather and a sister and brother) certainly pointed to a family linkage. Another patient whose eczema appeared early in life demonstrated a continuing dynamic factor of psychologic reaction to a life-long bodily condition of obesity, myopia and dysplastic build. This patient and another who had eczema since infancy showed a change in the localization and acuity of the eruption coincident with puberty and experientially related modifications of psychologic reaction and personality structure.

Coincident with the onset of eczema, the group whose eruptions began at or soon after adolescence universally showed precipitating experiences modifying and producing personality factors of varying degree. This was true also of coincidental experiences and psychologic reactions for persons whose periodic cutaneous manifestations or exacerbations were at all pronounced. There was no unanimity as to the character of the environmental situation or event or the effect or nature of its interpretation. Such factors as parental rejection, feelings of rejection, insecurity, sibling rivalry, failure of social experience or adaptation, broken homes, sudden growth and increased energy, stimulus of example and others were among the more commonly noted ones. In only 1 case were the sexual development and urge found to be dominantly dynamic. This was the case of a girl who demonstrated the sole true hysterical structure with repression and cyclothymic factors resulting in neurotic drive and the adoption of a remote difficult goal with continuous moderate frustration. Asthma also began at this period. The general result, on whatever basis or of whatever degree in these cases, was a decided and early channelization of drive into great purposefulness and the adoption of a difficult, remote or non-attainable goal. As would be expected, these persons showed a dynamic effect of the normal adolescent revolt and emancipation. This was most noticeable in subjects whose emancipation was delayed to the postadolescent period. In immediate situational dynamics, this group whose eczema appeared at adolescence showed predominantly or at least equally the effect of intrapsychic factors of personality as against environmental stress.

All 4 patients whose eruption first appeared in later years (late exudative diathesis) demonstrated the overwhelming weight of unique environmental stress as against varying but only

moderate personality factors of structure. In them the precipitating and apparently dynamic factors included for 1 a unique and stressful army experience, for the second, the demands of an enforced speed-up of condensed school experience due to induction into the Army and personal seriousness, for the third Army demands and recent marriage with unexpected separation, and for the fourth, childbirth, a dipsomaniac husband and the necessity for a decidedly feminine woman to fend for herself and to assume responsibility for her husband and son.

Psychopathologic changes of diagnostically appreciable degree were evident in 7 patients with atopic eczema—2 in the "infancy" group and 5 in the "adolescent" group and in none of the patients with late exudative diathesis. One of these patients had a loosely knit personality with schizoid tendencies, with shyness, self assertion and great social need, paranoid reaction, cyclic depression and reactive depression, hysterical reaction, and an obsessive compulsive reaction. Personality analysis revealed in certain aspects of personality, varying degrees of differences of apparent dynamic importance.

With 3 exceptions the subjects ranged from bright normal to very superior as measured by the Bellevue-Wechsler scale, Rorschach test, various other tests, vocabulary, school grades and achievements. This intelligence appeared somewhat weighted on the performance side as opposed to the verbal side in the non-neurotic subjects. Among those with eczema beginning in infancy were the 3 of lowest intelligence but even they were in the upper normal range. Very superior intelligence was encountered in the neurotic subjects of the "adolescent" group while the older group along with the normal personalities encountered in the "adolescent" group, were in the bright normal classification. Except for the 1 subject with schizoid personality and the 1 with hysterical reaction among those whose eruption appeared at adolescence, thinking tended to be concise and of the concrete and tangible variety rather than abstract, though increased abstract thinking was noted in the neurotic subjects of superior intelligence. No tendency to phantasy or unreality was noted except in the subject with hysterical reaction. Concentration and preoccupation were predominantly with material reality.

The outstanding emotional feature throughout was suppressed resentment, on which few subjects focused and which most had difficulty in verbalizing. When expressed, it varied from vague irritation and frustration found in the schizoid person to pronounced hostility, together with some guilt in the persons with paranoid re-

actions. The mood tended to be grudging, sorrowfully serious and in a few cases, depressed. Moods appeared rather persistent. Anxiety was relatively nonappreciable except in 1 of the "infancy" group, 1 of the "late" group and 1 of the "adolescent" group, the latter also giving a history of peptic ulcer. As previously noted, tension was universal. There was a tendency toward stubborn rigidity and high emotional reactivity masked by suppression. Superficially there was apparent emotional stability except in the subject with hysterical reaction and those with cyclothymic tendencies (3, also asthmatic). Action tended to be planned and limited sharply in direction. There was little spontaneity. These action tendencies were much greater in the neurotic group. A tendency to exactness and meticulousness coupled with relatively high standards was increased to perfectionism in the neurotic group. In the older group such action tendencies seemed forced on the individual by his seriousness and the situational exigencies. Coupled with high motivation, intense purposefulness and selection of difficult or unobtainable goals, these subjects all showed considerable self-exaction. Hypochondriasis or abnormal concern with the body was not evident except in 3 persons in whom asthma was associated and in all asthmatic persons (7), who showed a tendency to self-pity and self-punishment. The remaining patients seemed to have difficulty in focusing on even the physical need of their bodies. Self-assertiveness and social need were pronounced in the persons with atopic eczema and were greatest in those in whom it was associated with asthma and paranoid character. While in the main giving the appearance of considerable self-adequacy and efficiency, those with atopic eczema showed varying degrees of inability to get along with or effect adjustment with others. This lack appeared to depend on the exceeding purposefulness of the more normal persons with eczema first noted at adolescence, but in the neurotic persons it appeared to be defensive.

#### SUMMARY

Thirteen patients with atopic eczema and 4 with late exudative diathesis were studied by a dermatologist, an allergist and a psychiatrist. A definite psychosomatic relationship seemed apparent, and the cutaneous manifestations appeared to be evidence of psychobiologic disbalance in the reaction of the total individual.

Our findings are not incompatible with the more general ones reported earlier by van de Erve and Becker, though based on fewer subjects, more limited diagnostic categories and more specific individual reactions. The results



do not permit a generalized concept of a personality type. These results would support a concept of a relative and dynamic relationship in which constitution specific allergic sensitizations, personality and environmental stresses play roles of varying degree in each individual's total reaction.

Physical similarities were present first in the evidence of atopy in one or several forms usually associated with an atopic familial background. The persons with it were physically vigorous, had high pulse pressures and rapid pulse rates and responded well to exercise. The atopic persons were under normal weight. There was a tendency to vascular hypotension and lowered basal metabolic rate.

The majority of these persons presented psychologic and emotional characters allowing them to be classified as normal. Seven of the atopic patients presented psychopathologic changes of varying degrees. All of these had asthma or rhinitis in addition to their eczema. All the patients presented certain personality factors in common: suppression of resentment tension (which in some cases was masked) and more than average intelligence and self assertiveness. Certain other personality factors were commonly present but appeared to be of less importance. There was almost uniform absence of anxiety and hypochondriasis.

In almost all cases the onset of the eruption or its exacerbations was influenced by environmental factors, but in individual cases there were varying degrees of dependence on environmental stresses and personality constellation. In patients with late exudative diathesis there was overwhelming importance of environmental stress, though these persons too showed the psychologic common denominators of suppressed resentment tension, high intelligence and self assertiveness. In those with atopic eczema but without psychopathologic changes the intrapsychic factors and environmental stresses appeared to be of approximately equal importance. In the persons with atopic dermatitis and of neurotic character personality determination was so great as to make the intrapsychic factors almost all-important, leading to the assumption that almost any environment would have provided the dynamic stress necessary to engender the resentment and reaction. A generalization of personality type encompassing the highest trend of each variable would not fit any individual patient studied but would best approximate the points in common found in those patients with definite psychoneurotic structure and various psychopathologic changes. Typology, however, would represent a short cut of

thinking and encompass a fundamental fallacy contrary to these observations.

#### ABSTRACT OF DISCUSSION

DR S W BECKER, Chicago. I should like to express my personal appreciation for the excellent papers of Drs. Michelson and Lynch, Hinckley and Cowan on a timely subject. They make me feel like the missionary who had labored fruitlessly in foreign fields for many years but finally was rewarded by a convert.

One of the most important statements is that by Dr. Michelson, early in his presentation, that it is the patient who must be studied and treated and not merely the dermatosis. It would seem that until there is a universally accepted concept of the psyche the designation "neurosomatic" would be preferable to "psychosomatic." Definitions of the psyche vary from that of Dorland, who calls it "the mental life, including both conscious and subconscious processes," to that contained in a dictionary of psychiatry, which extends the psyche to the very terminations of the sympathetic nerves.

Many of the reactions mentioned, such as resentment of family conditions, are not specific to my way of thinking, but merely illustrate the intense intolerance of the hyperactive, hypersensitive patient.

The choice of self-inflicted lesions for study has the advantage mentioned by Dr. Michelson that the diagnosis may be made with a high degree of certainty, but it has the disadvantage that it is the only one of the neurodermatoses that I have sometimes seen in truly psychotic persons. This fact emphasizes the need of psychiatric management in treating some of the patients as contrasted to those with other neurodermatoses.

As the case histories were read over, they could, for the most part, have been those of patients with any of the functional cutaneous disorders. In other words, the patient who presents self-inflicted lesions is not greatly different fundamentally from the others. In one place the author mentions the "battling against the causes of their difficulties." Patients with functional cutaneous diseases are born battlers, veritable crusaders. Therapeutic substitution of "resignation" works wonders with them.

Dr. Lynch has presented a report of studies on a group of patients somewhat similar to one studied by Dr. van de Erve and me, although he also enlisted the aid of psychiatrists. My own efforts to obtain such cooperation extended over several years but were fruitless. He states that "the presence of tension does not prove a causal relationship with a patient's eruption," which is true, but one must admit that tension increases his exhaustion, which I believe is highly significant.

The failure to elicit a history of atopy in the families is not so difficult to explain, when it is realized that inherited tendencies must have a beginning. Repeated intermarriage of hyperactive, hypersensitive persons seems eventually to increase the protoplasmic unrest to the point at which allergic—or atopic, if one prefers that term—reactions may occur following contact with substances in the environment. I have never been able to convince myself, from my studies, that atopic dermatitis is allergic or atopic, which Dr. Lynch implies in one place.

The complaint of fatigue in 12 of his 17 patients does not conform with my experience. It is true that eventually such persons become bored with life and experience a sensation which they may interpret as fatigue, but my opinion is that they do not have a normal sense of fatigue which induces them to retire at the proper hour and obtain sufficient nocturnal rest.

Until the psychiatric study of patients with functional dermatoses has furnished a more substantial working basis for therapy, I shall continue to utilize a simpler



approach, one which has produced acceptable therapeutic results. The history obtained from my patients of a lack of normal sense of fatigue has suggested that the functional disease may result from a perversion of this sense, which normally should act as a brake on their activities and insure adequate rest. The patient is told that he must do what he would if he felt tired—rest.

The overactivity, mentioned by both authors, exhausts the body and, presumably, causes products of exhaustion. One would think that such products would stimulate nervous pathways which furnish the person with a sensation of fatigue, said by physiologists to be a proprioceptive phenomenon. However, this does not occur. These products of exhaustion can conceivably stimulate other pathways, which go to various parts of the body, and produce functional disease. I have seen extreme fatigability and a neurodermatosis alternate for months at a time without any treatment at all, and in all my patients a sense of fatigue develops as the functional dermatosis becomes less severe. Demonstration by Dale and Loewy of the release of acetylcholine and sympathin at nerve endings furnishes a sound basis for such reasoning. It is well known that there are nerve endings in the skin, including the epidermis, which could theoretically be the sites of formation of chemical substances capable of producing the dermatoses. Dr. Nomland has just discussed cholinergic urticaria and itching.

Then, too, the patients are just as hypersensitive as they are hyperactive. Their oversensitivity induces abnormally strong emotional reactions, which aggravate the exhaustion. It is here that the psychiatrist has a legitimate interest in the problem, but I am not convinced that any of the neurodermatoses occur anywhere near 50 per cent of instances following some specific psychic reaction.

It is hoped that the authors will extend their excellent studies to other functional diseases of the skin.

DR JOSEPH V. KLAUDER, Philadelphia. It is interesting to note the increasing importance given to psychosomatic relations in medicine. Although the term is new, its connotation is certainly not. The term is, so to speak, a new jar for old wine. In the works of Plato appears the statement: "The great error of our day in the treatment of the human body, that physicians separate the soul from the body." Socrates could not cure Charmide's headache unless his soul as well as his body was treated. And in Hyde and Montgomery's textbook on dermatology, published some years ago, the authors said, "The widow must set aside her veil beneath which her urticaria plays."

It seems to me that that simply expresses a concept that old practitioners of medicine appreciated, without the use of new words and many complicated hypotheses.

Menninger, I think, has a different concept of neurotic excoriations than dermatologists have. He conceives the manifestation as a form of focal suicide, an attempt to destroy the ego (Menninger, Karl A. *Man Against Himself*, New York, Harcourt Brace and Company, Inc., 1938, pp. 234-248).

I do not believe that all neurotic excoriations can be classified in one group, since the psychogenesis is variable (Klauder, J. V. *Psychogenic Aspects of Skin Diseases*, *J. Nerv. & Ment. Dis.* 84: 249-273 [Sept.] 1936). Frequently the condition is an expression of a phobia, usually the fear of parasites. In other instances it may be classed among the topalgias of Brocq or with what Janet has called *l'obsession de la honte du corps*. This particularly applies to the excoriated acne of young girls. In still other cases the practice may be the expression of a displacement. Manipulation of the skin is performed at times after mental stress and strain and after an emotional upset. In cases of pronounced

neurotic excoriations, the psychogenesis is not easily determined and the cure not easily effected.

The increasing incidence of psychoneurosis has been stated by some writers to be a threat to civilization. Some of them mention an incidence of psychosomatic symptoms as high as 50 per cent in various fields in the practice of medicine.

I was curious to know about what is the incidence in the practice of dermatology, and so I studied 14 consecutive case records of private patients and charted and analyzed them. The disease of the skin in 12 per cent of this number was regarded as having a psychosomatic relation. If the doubtful cases were included the incidence would be 15 per cent. The incidence of psychosomatic expressions in diseases of the skin is in relation to the broadness of one's concept of psychosomatic relations and difficulty in deciding where normal reactions end and abnormal ones begin. For example, should one include in the category of patients with psychosomatic diseases those who have an abnormal reaction to their disease? What constitutes an abnormal reaction? Again, should patients be included in which itching or other subjective symptoms are out of proportion to the degree or severity of the disease? Again, it is difficult to evaluate the range of normal subjective symptoms.

DR SAMUEL M. PECK, Bethesda, Md. I should like to discuss the papers of Michelson, Lanch, Hinch and Cowan together.

Dr. Michelson's paper seems to me to illustrate clear-cut examples of dermatologic diseases in which a proper diagnosis was made and the dermatologic lesions were found to be secondary to a primary psychiatric disturbance. It was perfectly proper, therefore, once the basic condition was established to leave further therapy in the hands of the psychiatrist.

The second paper, however, does not present such a group of cases. Psychiatric treatment is suggested as the main approach to the problem of therapy before exhaustion of all possible diagnostic aids to rule out true organic disturbance. This does not mean that psychiatric treatment should not be attempted as adjuvant to other therapeutic measures in cases in which the psyche of the patient plays a definite role in the organic disturbance.

There are fads in medicine, and the very term "psychosomatic" places the wrong emphasis of the method of approach in investigating the cause of a disease such as atopic eczema. I suggest for its psychological effect that one speak of somatopsychic studies in dermatology so that proper emphasis can be placed on the role of the psyche in the study both of the cause and of the therapy of a cutaneous disease.

DR HOWARD FOX, New York. I should like to discuss Dr. Lanch about a certain feature of atopic eczema (disseminated neurodermatitis) which has bothered me for a long time. This relates to the good-natured, kindly outlook on life of these patients in spite of extreme itching at times, which interferes with sleep. Not to mention attacks of hay fever or asthma.

Cases of this disease run so true to form, from the standpoint of history, appearance and location of the eruption, that the diagnosis, at least, is usually easy. I have long noted that the majority of the patients are well nourished, are usually above the average mentality and almost invariably show the kindly disposition I have mentioned. They have the appearance of persons with a good disposition, and their immediate relatives invariably agree that such a disposition exists. When persons who are so easily upset or annoyed by trifling circumstances and who often fear their skin ferociously can have a good outlook on life is most

than I can understand I have never heard a discussion of this particular question, and I should like Dr Lynch to explain it

DR C GUY LANE, Boston I imagine that Dr Lynch, in his review of the literature, found the series of some 30 cases observed by psychiatrists at the Massachusetts General Hospital several years ago, cases of atopic dermatitis which were studied for a considerable time Several of the graphs included in that article showed striking relationship of the attacks of neurodermatitis to some psychic event occurring in the lives of these patients As I remember, in that article Fine-singer and Greenhill agreed, too, that the two factors of resentment and anger played the largest part in the causation I think that in that article, also, the term "emotionally not stable" was used rather than the term "emotionally unstable"

In my opinion, in cases such as these rest, reassurance and reeducation are valuable items in regard to helping the patients

DR SAMUEL AYRES JR, Los Angeles I should like to support what Dr Peck said, without in any way detracting from the extreme importance of Dr Becker's work and the papers of Dr Lynch and Dr Michelson, because only too frequently the two factors, the psychic and the somatic, are both involved

It calls to my attention a young man whom I have followed from infancy, with a severe atopic dermatitis, the son of a physician who died some years ago

This young man from infancy on has been highly sensitive to egg, wheat, and one or two other things As long as the diet is properly adjusted, his skin is in good condition He finally got into the Army, and had never been so happy in his life He thoroughly enjoyed his Army existence and his uniform, and yet began to break out with a tremendous exacerbation of his atopic dermatitis to the extent that he had to be discharged from the Army That was one factor in his discharge

The other factor was that there was a history, which was discovered, of dementia precox which had been successfully treated As soon as the patient returned home and was put on proper diet, his eczema improved and his skin remained in good condition

He was employed in one of the war plants and was having no trouble whatsoever until one day he found himself in jail, whereupon he had a severe exacerbation He was in jail for about five days The reason he was in jail was that he was caught wearing his uniform

Now, I might have said that these two exacerbations were due to the psychic effects of being in the Army and in jail, but, on the other hand, as it turned out, the food he was getting in the Army and in jail consisted of those things to which he was highly sensitive I think that one must not get too far afield and forget that there are definite and concrete and tangible factors involved in many of these cases We dermatologists must keep a balance, recognizing the psychic background but not forgetting that there are other parts of the background

DR CARROLL S WRIGHT, Philadelphia I should like to rise in defense of this term "psychosomatic" Because of having presented a paper at New Orleans this winter on the subject, I feel that I should perhaps say one or two words about it It seems to me this is an excellent term

All admit that in a great many diseases there are both the psychic and the somatic factor Patients object to being called "neurotic" or something else that even suggest that their disease may be a neurosis, but they do not seem to object when one tells them that they have a combined psychic and somatic disturbance

Also, referring physicians rather like this term, perhaps because it happens to be a popular one at present

I feel that if we dermatologists take an antagonistic attitude toward it, we are going to be criticized, just as Dr O'Leary and Dr Sulzberger have been criticized by neurologists for fighting the idea of the possibility that emotional changes are a cause of some cutaneous disturbances

I think that Flanders put it well when she said that physicians criticize the Christian Scientists because they will not accept the somatic component of disease and that physicians are going to be subject to the same criticism if they do not accept the psychic component of disease

DR JOSEPH GRINDON SR, St Louis While I quite agree with Dr Michelson that dermatitis factitia and neurotic excoriations present a great deal in common and in some cases the two conditions overlap, yet it seems to me that one should draw a sharp distinction between them

Neurotic excoriations in many cases are simply an outcome of a common bad habit Many persons finger their faces while they talk Oftentimes this has a physical basis Acne, as was remarked, is one of the chief underlying causes The patient is apt to finger the face, and in that way he aggravates the disease by picking at the lesions, causing them to spread

Dermatitis factitia is different, and the patients with it can be classified pretty definitely in three groups

In the first place, there are the definitely insane persons, such as inmates of asylums Their lesions are often about the scapular region, but at times they are on the face or trunk

A man of this sort, an inmate of the St Louis City Sanatorium, an insane asylum, dug deeply into his skin in various places, producing very ugly sores He acknowledged that he did it purposely, because he was being shot with "electric needles" carrying poison and he had to dig out the poison But he said there was one source of consolation At a certain place in the asylum there was a hole, and there he could look deep down into hell and see his persecutors being tortured, a considerable alleviation to his feelings

The second group is composed of hysterical persons I do not know what else to call them A young woman was referred to me for peculiar cutaneous ulcers which had not been diagnosed It was clear from their outlines and their history that they had been self inflicted I so told the physician who had referred the patient to me He said that they could not be But soon thereafter the patient called again and over her left deltoid muscle was an ulcer forming a perfect five pointed star and beside it another of the shape of a crescent moon, the two together making a good copy of the Turkish standard

Patients of the third group are fairly intelligent, they main themselves deliberately, as a matter of deceit, to obtain a desired end About 9 o'clock one night a woman telephoned asking me to go to see her daughter, 16 years old, who was attending boarding school She was bleeding from her legs A teacher, acting as amateur nurse, had applied many layers of towels I removed one after another and finally came down to the last one, on which was a little speck of alleged blood Inspection of the leg showed a scratch inflicted with a pin or possibly with a finger nail, but there was something queer about the color of that blood It so happened I had some patients who were china painters, and I had become familiar with the pigments which they used I found that the girl was studying china painting When pressed for a reason for her actions, she admitted that she had merely been trying to be sent home

DR HENRY E. MICHELSON, Minneapolis. We knew when we proposed to present this subject that there would be considerable discussion.

One must realize that when one is trying to analyze the motivation of human acts there is no one guide to follow. Psychiatrists are not agreed on many of the basic principles involving behavior, and therefore one should be receptive to new ideas.

You may have noticed that Dr Becker speaks of "these people," which for him includes a large group, and his approach to such varying diseases as neurodermatitis and alopecia areata is quite the same. I differ in this respect, that I believe that one cannot so group these diseases etiologically but should be alert enough to recognize this group of people early in an interview and then attempt to find out if possible underlying reasons which may account for the dermatosis or other trouble. Certainly the approach alone cannot be enough.

Dr Klauder mentioned hysteria, which is more or less an entity, and one must not glibly use the word hysteria to apply to neurotic excoriations.

I do not believe that Dr Peck or any other dermatologist needs to worry about losing his patients with acne to a psychiatrist. If we dermatologists could only learn to treat acne psychically as well as dermatologically, we would be in a much better position to aid patients with the disease.

DR FRANCIS W. LITCH, St Paul. As Dr Michelson said we appreciate the sincerity and variety of comments. We did not expect complete agreement.

Dr Wright's discussion raised the question of terminology, which is an important one. If there is to be a mutual understanding of psychosomatic relationships in dermatology dermatologists must have some understanding of the terms and classifications used by psychiatrists. All dermatologic patients can be placed in three main groups: first those in whom the somatic, or physical factor is all-important or practically all-important, second, those in whom the psychic and emotional factors and the physical factors are roughly equal but of varying degrees of importance, and, third, those in whom psychic and emotional changes are practically all-important. Within this last group are three main divisions: psychotic persons, psychoneurotic persons and persons with so-called psychosomatic disturbances. Dr Michelson's patients fell chiefly in the group of psychotic persons and partly in the group of psychoneurotic ones. I was not concerned with psychoses in my discussion today but was concerned with some psychoneurotic subjects. Some of them have asthma and associated with their asthma, many have eczema. Most eczematous individuals may be regarded as normal persons (neither psychotic nor psychoneurotic) who

have psychosomatic disturbances. The term "psychosomatic" is useful because most physicians understand what is meant, but the word may be open to criticism and many psychiatrists prefer other terms.

Dr Fox brought up the question of the value of these individuals. They are good citizens, they have high moral standards, they are meticulous—in fact, many of them are perfectionists—but there is a lack of spontaneity. Many of their pleasing characteristics result from deliberate and conscious effort to make themselves good citizens. They are likely not to be naturally gregarious.

Dr Peck's question about who shall treat these patients was answered to some extent by Dr Michelson. I certainly do not intend to give up my patients with eczema, but in certain cases if I can get real help from a psychiatrist I am not going to refuse this help. In a large proportion of these cases, I believe I can advantageously use a psychiatric approach, not regarding myself in any sense as a psychiatrist. If we dermatologists have some appreciation and sympathy for the psychologic and emotional changes in these persons, I think it may help us in the treatment of many patients with eczema, probably in more instances than we are helped by the allergic approach.

Dr Lane mentioned the presence of hostility and anger, reported by Greenhill and Finesinger, in a group of patients who had all had eczema in infancy (ARCH. DERMAT. & SYPH. 46:187 [Aug.] 1942). It is our belief that the existence of the emotions is less important than the suppression of resentment by these persons. Here lies the difference between our patients and those of Dr Michelson. Suppression calls for a conscious effort on the part of the patient. In Dr Michelson's patients the same or different emotions have led to repression, which occurs unconsciously in psychotic and severely psychoneurotic persons.

Again I wish to point out that in this group of eczematous individuals there was present a group of characteristics. Constitutional factors were evident by virtue of the presence of atopy. Of the physical factors the most striking was the high degree of physical vigor. Environmental factors were of varying degrees of importance in different cases. In the present study our chief interest lay in the psychologic and emotional factors, but we do not suggest a lack of importance of the other factors just enumerated. Of the personality factors the more significant appeared to be: (1) suppression of resentment, (2) the presence of tension (in some cases decided), (3) more than average intelligence and (4) self assertiveness. While some of these patients were neurotic, the majority can be regarded as psychologically and emotionally normal.

## PAPULAR SPOROTRICHOSIS

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According to de Beurmann and Gougerot<sup>1</sup> papular dermic sporotrichosis may be divided into papular, papulopustular and papuloulcerative types. They state that the cutaneous lesions are usually associated with mixed polymorphic sporotrichoses and rarely occur alone. In our case, the lesions were exclusively papular. During the course of three years, the papular aspect of the lesions was not modified.



Fig 1—Papular sporotrichosis

In the United States dermic sporotrichosis has been reported by Mount<sup>2</sup>. Uncomplicated sporotrichosis has not previously been reported in Brazil. The papulopustular acneiform variety has been reported by Aleixo<sup>3</sup> and Martins de Castro<sup>4</sup>. In the case reported by Martins

1 de Beurmann, C L, and Gougerot, H. Les sporotrichoses, Paris, F Alcan, 1912, p 300

2 Mount, L B. Sporotrichosis, Arch Dermat & Syph 25 528-534 (March) 1932

3 Aleixo, A. Dermatomycoses em Belo Horizonte, in Congresso sul americano de dermatologia e sifilologia, Rio de Janeiro, Imprensa Nacional, 1921, p 294

4 Martins de Castro, A, cited by Almeida, F P. Medical Mycology, São Paulo, Empresa Melhoramentos de São Paulo, 1939, p 631

de Castro<sup>4</sup> the lesions were purely pustular, while in that of Aleixo<sup>3</sup> other sporotrichotic lesions were present, constituting a mixed type. Sutton and Sutton<sup>5</sup> have stated that dermic sporotrichosis is rare in the United States, and this accords with the observations for Brazil. The differential diagnosis must be made between this disease and erythematous lupus, leprosy, syphilis and mucocutaneous (American) leishmaniasis. Treatment was carried out with potassium iodide in 4 grain (0.26 Gm) daily

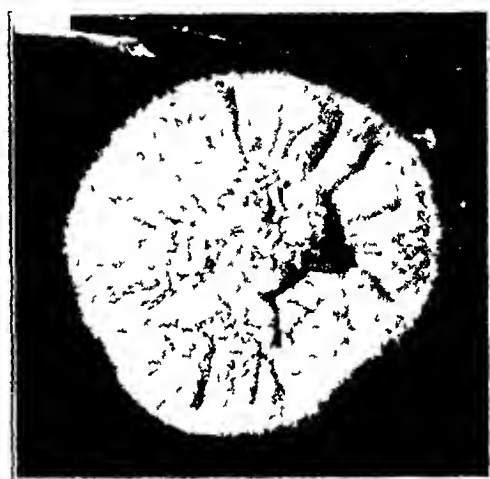


Fig 2—Culture of *Sporotrichum schenckii*

doses. The disease yielded promptly to treatment and disappeared completely in ten days.

### REPORT OF A CASE

A S, a Brazilian mulatto, was a farmer living at Ponte Nova. The family and personal antecedents were irrelevant. The patient stated that three years ago there appeared on the left side of the nasal pyramid a small nonpruritic papule, dark brown and hard and with a smooth surface. Later, other identical lesions appeared and the eruption spread until it attained its present aspect and dimensions.

Physical examination showed nothing abnormal. On dermatologic examination, there were seen numerous papules on the dorsum and left side of the nasal pyramid. Some of these were scattered, and others were confluent, a few were milium and others of larger size.

5 Sutton, R L, and Sutton, R L, Jr. Diseases of the Skin, St Louis, C V Mosby Company, 1939, p 1169

The outline of these papules was irregular, but the edges were sharply defined. Some papules were oval, others were rounded and of a pale violet color. The surface was slightly squamous. No exudation of any kind was noted. Sensation in all its three modalities was normal. No satellite adenopathy was noted. The lesions did not disappear on diascopic pressure. They roughly resembled flat warts (fig 1).

Results of examinations for acid-fast bacilli and leishmanias were negative. The Wassermann and Kahn reactions of the blood were negative. The Montenegro test for leishmaniasis was also negative. The cutireac-

irregular. The basal layer was deeply pigmented, but the amount of melanin was less at the level of the rete pegs. There were also seen in the rete malpighii areas of exocytosis, particularly in one of the specimens. There was definite hyperplasia of the sebaceous glands. At the level of the papillary and reticular layers, there was a dense inflammatory infiltration, which was somewhat diffuse and consisted principally of lymphocytes, plasma cells, histiocytes, polymorphonuclear neutrophils, some eosinophils and giant cells of the Langhans type. This infiltrate appeared under the form of tuberculoid granulomas (fig 3), at the level of which a form of



Fig 3—Histologic structure of a tuberculoid granuloma

tion to tuberculin was negative. Cultures were positive for *Sporotrichum schenckii* (fig 2).

One of us (M. A. J.) made the histologic examination. Two fragments of skin were taken from different parts of the area but the microscopic aspect of both was much alike. There was no thickening of the corneal layer at the level of which small areas of parakeratosis were observed and sometimes cellular remains were seen in the laminae.

The rete malpighii showed definite hyperplasia, and various pegs of the rete were seen, long, wide and

necrosis was observed. In one of the specimens the giant cell reaction was more pronounced than in the other.

#### SUMMARY

A patient reported for treatment for exclusively papular sporotrichosis. This type of sporotrichosis is rare. Cure was easily effected by the use of potassium iodide.

Rua Ceara, 1695



## HERPES ZOSTER GENERALISATUS ASSOCIATED WITH CHRONIC LYMPHATIC LEUKEMIA

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Herpes zoster in its common form, involving one side of the body and manifested by grouped umbilicated vesicles on an erythematous base, is a disease which many patients are able to diagnose.

Often, in addition to the zonal distribution of the herpes zoster eruption, umbilicated vesicles ranging in number from five to thirty may appear at various sites remote from the initial lesions, usually concurrently on the trunk. These widespread lesions were first described by Tenneson,<sup>1</sup> in 1893, as *vesiculae aberrantes*. He concluded that 90 per cent of patients who had herpes zoster presented these lesions, an opinion not shared by Barker.<sup>2</sup> Bluefarb and Morris<sup>3</sup> found them in 66 per cent of their patients.

A rarer manifestation of herpes zoster is known as herpes zoster generalisatus, in which scores or even hundreds of umbilicated vesicles appear in a widely generalized distribution over the body in conjunction with the classic zonal eruption of the disease. Haslund (cited by Parounagian and Goodman<sup>4</sup>) described the first case of generalized herpes zoster in 1897. Since that time a large number of cases have been reported.

The frequent occurrence of herpes zoster among patients suffering from leukemia, Hodgkin's disease and lymphosarcoma is a phenomenon which has drawn the attention of many investigators. Craver and Haagensen<sup>5</sup> stated

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1 Tenneson, H. *Traité clinique de dermatologie*, Paris, O. Doin, 1893, p. 116.

2 Barker, L. P. Generalized Herpes Zoster. Report of Nine Cases, *Arch Dermat & Syph* **40** 974-986 (Dec) 1939.

3 Bluefarb, S. M., and Morris, G. E. Herpes Zoster with Aberrant Vesicles. Report of Twenty Cases, *Arch Dermat & Syph* **43** 385 (Feb) 1941.

4 Parounagian, M. B., and Goodman, H. Herpes Zoster Generalisatus, *Arch Dermat & Syph* **7** 439-451 (April) 1923.

5 Craver, L. F., and Haagensen, C. D. Note on the Occurrence of Herpes Zoster in Hodgkin's Disease

that herpes zoster was more common in patients with lymphoblastoma than in the population at large. Ferreira<sup>6</sup> enumerated 42 cases in which herpes zoster and leukemia appeared concurrently. Of the 42 cases, 34 were instances of lymphatic leukemia, 3 of aleukemic leukemia (lymphatic type), 3 of myeloid leukemia and 2 of an undetermined type. It is interesting to note that of the 42 case reports listed only 38 included an adequate description of the extent of the lesions, and of these, 23 were of the herpes zoster generalisatus type.

Bafverstedt<sup>7</sup> added 3 more cases to the literature. He found that of the cases reported in which herpes zoster and leukemia occurred together, more than 58 per cent were of the generalized type of herpes zoster.

Recently Wile and Holman,<sup>8</sup> in an excellent review of the literature, surveyed the reported cases of generalized herpes zoster associated with leukemia, enumerating 32 cases and adding 2 of their own. Both of their patients were men who had lymphatic leukemia.

Recently we had the opportunity of studying a patient who had generalized herpes zoster and chronic lymphatic leukemia.

### REPORT OF A CASE

The patient, a white man aged 52, a printer, had been well until Jan 15, 1943, at which time acute edema of the tissues surrounding the right eye developed, with pain involving the entire right side of the head. The following day discrete lesions appeared on the face, and two days later similar discrete lesions appeared elsewhere on the body. Pain and burning sensations on the right side of the head were severe, and within another two days pustules made their appearance in

Lymphosarcoma, and the Leukemias, *Am J Cancer* **16** 502-514 (May) 1932.

6 Ferreira, M. J. Herpes zoster generalisatus bei Leukämie, *Arch f Dermat u Syph* **176** 295-308, 1937.

7 Bafverstedt, B. Herpes zoster generalisatus und leukämische Lymphadenose (kasuistischer Bericht), *Acta dermat-venereol* **21** 60-69 (Feb) 1940.

8 Wile, U. J., and Holman, H. H. Generalized Herpes Zoster Associated with Leukemia, *Arch Dermat & Syph* **42** 587-592 (Oct) 1940.



the lesions. There was no pain associated with the generalized eruption.

On March 16, 1943, the patient was seen at the Mayo Clinic. His only complaint was of persistent pain and swelling about his right eye. His general health had been excellent and his appetite unimpaired. He had previously suffered no loss of weight, no chills, no fever, no sweats and no loss of strength. For the preceding twenty-five years he had been troubled with hay fever, coming on annually between August 15 and September 15. For the past five years he had had asthma.

Examination of the patient disclosed a sharply delineated zone of edema occupying the distribution of the ophthalmic and maxillary branches of the trigeminal nerve on the right side. Scarring was prominent. The eyelids on the right could not be separated without pulling them apart manually. There were no vesicles or pustules present, but thickly distributed through the right side of the scalp and forehead were numerous firm nodules of the size of a lentil, each with an umbilicated center. These were arranged in small groups.

Scattered over the left side of the face and neck as well as on the trunk and extremities and appearing on a nonerythematous base were more than one hundred firm nodules of the size of a lentil, many showing clearcut umbilication centrally. These showed no tendency toward grouping nor was there any edema of the skin surrounding them.

The axillary and inguinal lymph nodes were almost as large as a walnut, and the spleen was palpable. Staining the right cornea with fluorescein revealed a slight corneal ulceration in addition to mild iridocyclitis.

Studies of the blood revealed 10 Gm of hemoglobin per hundred cubic centimeters. Leukocytes numbered 327,000 per cubic millimeter, with 92 per cent lymphocytes, 4 per cent neutrophils, 1 per cent basophils and 3 per cent immature lymphocytes. Erythrocytes numbered 3,980,000 per cubic millimeter. The urine was normal. The serologic reaction of the blood for syphilis was reported as negative. A roentgenogram of the thorax revealed a substernal goiter on the left with deviation of the trachea to the right.

Two pieces of tissue were taken for microscopic examination. One was from a group of lesions on the right side of the face; the other, from a solitary lesion on the left side of the thorax anteriorly. In the two specimens the histopathologic picture was the same, the outstanding pathologic features being more prominent in the former than in the latter. Hyperkeratosis without parakeratosis was noted in an epidermis which had lost most of its rete pegs. The rete layer was greatly thinned but otherwise was normal. There was increased melanin pigment in the basal cell layer. In the cutis large, dense masses of cellular infiltrate were noticeable. For the most part, these were arranged perivascularly, but hair follicles and sweat and sebaceous glands served also as focal points for the infiltrate. Scrutiny of the infiltrate under high magnification revealed a uniform type of cell, the cell being a large mature lymphocyte. Mitotic figures were not seen in these cells. Of unusual interest was the large number of foreign body, multinucleated giant cells lying within the infiltrated zones. These were present only in papillary portions of the cutis, especially in the vicinity of hair follicles. A sharply demarcated clear zone lay between the epidermis and the infiltrated portion of the dermis.

#### COMMENT

A review of the literature has rewarded us with but six other instances in which a lymphatic

leukemic infiltrate was demonstrated microscopically in the zosteriform lesion.

Jadassohn's<sup>9</sup> patient was a man, aged 68, who had lymphatic leukemia. Unilateral herpes zoster developed in the distribution of the first and second branches of the fifth nerve and subsequently became generalized.

Halle's<sup>10</sup> patient was a man, aged 71, who had lymphatic leukemia. Herpes zoster developed on the right side in the region of the sacrum and gluteal area and upper portion of the thigh and later involved the right side of the penis.

Gotttron and Jakobi<sup>11</sup> reported the case of a man, aged 63, who had subleukemic lymphadenosis. Generalized herpes zoster developed.

Katz's<sup>12</sup> patient was a woman, aged 49, who had lymphatic leukemia. Herpes zoster was first confined to the right cheek and right side of the neck and thorax down to the third rib, but later it became generalized.

Freund<sup>13</sup> described the case of a woman, aged 57, who had lymphatic leukemia of two months' duration. Herpes zoster was present on the left side of the head and neck. The generalized eruption developed later.

Barney's<sup>14</sup> patient was a man, aged 64, who had lymphatic leukemia of two and a half years' duration. Unilateral herpes zoster developed on the thorax.

In all of these cases definite evidence of leukemic infiltrate was observed in the microscopic sections, and in some, as in Barney's, the infiltrate was noted six months after the initial appearance of the herpes zoster.

A finding of interest in Jadassohn's, Halle's, Barney's and our case was the large number of multinucleated, foreign body giant cells. These are seen fairly frequently in leukemia cutis and were described by Nicolau<sup>15</sup> in 1904.

9 Jadassohn, J. Leukämische Infiltrate in Zosterarben, *Zentralbl f Haut- u Geschlechtskr* **20** 741, 1926.

10 Halle, H. Zoster und Leukämie, nebst Bemerkungen über die Provokation leukämischer Infiltrate in der Haut, *Arch f Dermat u Syph* **159** 238-249, 1930.

11 Gotttron and Jakobi. Subleukämische Lymphadenosis cutis nach Herpes zoster generalisatus, *Zentralbl f Haut- u Geschlechtskr* **32** 548, 1930.

12 Katz, F. Zoster bei Leukämie, *Arch f Dermat u Syph* **164** 561-564, 1932.

13 Freund, H. Zoster und Leukämie. Ein Beitrag zur Kenntnis des symptomatischen Zoster, *Arch f Dermat u Syph* **154** 476-489, 1928.

14 Barney, R. E. Zosteriform Leukämia Cutis, *Arch Dermat & Syph* **37** 238-246 (Feb) 1938.

15 Nicolau. Contribution a l'étude clinique et histologique des manifestations cutanées de la leucémie et de la pseudo-leucémie, *Ann de dermat et syph* **35** 753-796, 1904.

He expressed the opinion that they bore a relationship to the disintegration of hair follicles occurring in the process of leukemic infiltration.

In our case, as in that reported by Bafverstedt, it was the generalized herpes zoster which caused the patient to seek medical attention and thus led to the discovery of the more serious condition of the blood. That herpes zoster generalisatus occurs in the absence of leukemia or other diseases of the lymphoblastomatous group is attested by the cases reported by Barker<sup>2</sup> Grindon<sup>16</sup> and others. However, the generalized form of herpes zoster is relatively rare, and in a large number of the cases reported it was associated with leukemia, particularly of the lymphatic type.

It is, of course, inviting to speculate on the reason for the occurrence of a leukemic infiltrate in the lesions of herpes zoster. Halle,<sup>10</sup> as well as Foerster<sup>17</sup> and Keim,<sup>18</sup> expressed the opinion that the herpetic lesion is merely the traumatic stimulus which causes an influx of leukemic

infiltrate into the affected site. We concur in this view. Thus in Foerster's case, that of a boy who had had varicella, acute lymphatic leukemia subsequently developed. Biopsy of a specimen taken from the site of a healed varicella lesion revealed leukemic infiltrate, and biopsy of a specimen taken from apparently normal skin likewise revealed leukemic infiltrate but to a lesser degree.

Keim's<sup>18</sup> remarks are appropos: "If the skin contained such microscopic infiltration, the inflammatory reaction produced by the herpetic lesion might readily result in such an outpouring of lymphatic cells as to produce true lymphatic infiltrates along the course and distribution of a simple herpes zoster."

#### SUMMARY AND CONCLUSIONS

A case was observed in which generalized herpes zoster occurred in association with chronic lymphatic leukemia. The zosteriform lesions were suggestive of a true leukemic infiltrate. A review of similar cases in the literature reveals that they are relatively rare. Generalized herpes zoster may be the presenting symptom and sign of chronic lymphatic leukemia.

16 Grindon, J., Jr. Herpes Zoster with Generalized Eruption. Report of Three Cases, *Arch Dermat & Syph* 39 865-866 (May) 1939.

17 Foerster, H. R., in discussion on Barney,<sup>14</sup> p. 245.

18 Keim, H. L., in discussion on Barney,<sup>14</sup> p. 246.

# NUTRITIONAL SURVEY OF THREE HUNDRED AND FIFTY-FOUR DERMATOLOGIC PATIENTS\*

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DURHAM, N C

Since the skin frequently shows signs that are attributed to dietary deficiency, it seemed desirable to survey patients with various dermatologic conditions to determine what part, if any, their dietary status played in the production of their cutaneous diseases. At Duke Hospital in the nine month period from October 1942 to June 1943, 354 patients seen in the dermatologic clinic were studied for physical signs and biochemical changes in the blood suggesting nutritional disease or preclinical deficiency. These data are presented herein, with analyses made on a seasonal basis for the group as a whole and by specific disease when 3 or more patients had the same clinical picture. The laboratory tests were made only on the blood and included determinations of ascorbic acid, vitamin A, carotene and hemoglobin and red blood cell counts, hematocrit readings and calculation of mean corpuscular volume, mean corpuscular hemoglobin content and mean corpuscular hemoglobin.

The dietary data were confined to a questionnaire filled in for each patient by the staff of the clinic at the time of the visit to the hospital. The resultant dietary information was uneven and not readily reducible to definite figures. In general, the patients gave histories of diets typical of this region, and these were not grossly inadequate except by extremely high dietary standards.

Altogether seventy-one separate diagnoses were made for the 354 patients herein reported on. There were 303 white and 51 Negro patients. The clinical dermatologic diagnoses with the number of patients studied included: syphilis 50, contact dermatitis 38, neurodermatosis 29, dermatophytosis 28, stasis dermatitis with bacterid 24, psoriasis 22, pyoderma 20, acne vulgaris 18, dermatophytosis with dermatophytid 16, seborrheic dermatitis 14, chronic discoid lupus

erythematosus 10, stasis dermatitis 10, dermatitis medicamentosa 9, erythema multiforme 8, eczematous dermatitis 8, urticaria 6, ichthyosis 4, epithelioma 4, scleroderma 4, lupus erythematosus disseminatus 3, pemphigus vulgaris 2, blastomycosis 2 and others (single diseases) 2.

## LABORATORY METHODS

Determinations of vitamin A, ascorbic acid, carotene and hemoglobin were made by means of the Evelyn photoelectric colorimeter. Mindlin and Butler's<sup>1</sup> method was used for determining amounts of ascorbic acid in the plasma, with Tillman's dye and a 2 cc sample. Vitamin A and carotene were determined by Kimble's procedure. Hematocrit determinations were made with the Wintrobe tube.

## RESULTS

In table 1 are shown the laboratory findings by season for the entire group of 303 white patients. It is interesting to note that there were no essential seasonal variations.

TABLE 1—*Seasonal Distribution of Blood Findings in 303 White Dermatologic Patients*

	Fall 1942	Winter 1943	Spring 1943
Number of patients	153	75	75
Mean Levels for Group			
Plasma vitamin C mg	0.45	0.45	0.46
Plasma vitamin A U S P units	92	87	84
Plasma carotene, U S P units of vitamin A	243	222	255
Hemoglobin, Gm	14.0	13.6	13.3
Red blood cells, millions	4.6	4.5	4.5

Table 2 shows the vitamin levels by disease for all diagnoses for which 3 or more patients were listed.

1 Mindlin, R. L., and Butler, A. M. The Determination of Ascorbic Acid in Plasma. *Macromethods and Micromethods*, J. Biol. Chem. **122**: 673-686 (Feb.) 1938.

2 Kimble, M. S. The Photocolorimetric Determination of Vitamin A and Carotene in Human Plasma. *J. Lab. & Clin. Med.* **24**: 1055-1065 (July) 1939.

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*Plasma Ascorbic Acid* Mean levels show no seasonal variation, being 0.45 mg per hundred cubic centimeters of plasma in each of the three seasons. This level agrees with the usual findings in field surveys in North Carolina except for the absence of a drop in the spring. The absence of this drop probably indicates a fairly high economic level for this entire group. The mean, however, fails to indicate the extremes that were found. Forty of 354 patients (11 per cent of the group) had zero levels of ascorbic acid, and 97 (27.5 per cent of the group) had 0.2 or 0.3 mg per hundred cubic centimeters. This picture also is characteristic of the dietary status of this region.

between those of the two groups mentioned. It would be of interest to make determinations for a much larger group of patients with urticaria to study the possible role of ascorbic acid in its manifestations.

Interestingly, the plasma levels of ascorbic acid of women were about double those of men with the exception of 10 persons with lupus erythematosus of the discoid type, for whom the male average was five times that of the female.

*Vitamin A and Carotene* These elements are of special interest in a consideration of cutaneous diseases, since vitamin A has a specific function in the nutrition of epithelial tissues. Here again, as shown in table 1, the mean plasma

TABLE 2—Mean Blood Levels of Vitamins and Hematologic Data for Patients with Common Dermatoses

	Number of Patients	Vitamin C, Mg	Mean Plasma Levels				Hematologic Values			
			Vitamin A, U S P Units	Carotene, U S P Units †	Hemoglobin, Gm	R B C, Millions	Hematocrit	M C V	M C H	M C H C
Contact dermatitis	38	0.40	90	229	13.9	4.47	40.0	90	31	34
Neurodermatoses	29	0.43	88	222	13.4	4.60	40.2	87	28	33
Dermatophytosis	28	0.36	92	236	14.7	4.71	43.3	92	31	34
Dermatophytosis with dermatophytid	16	0.37	87	196	13.7	4.60	41.4	90	30	33
Syphilis										
Neurosyphilis (under therapy)	26	0.35	94	271	13.5	4.41	39.9	90	30	33
Latent syphilis (under therapy)	20	0.42	80	210	12.1	4.26	37.1	82	27	32
Primary and secondary syphilis *	4	0.32	56	216	11.0	4.05	34.0	84	27	32
Stasis dermatitis with bacterid	24	0.32	85	197	13.2	4.46	39.6	88	29	33
Stasis dermatitis	10	0.39	90	247	13.0	4.42	39.4	89	29	33
Poriasis	22	0.40	91	197	15.4	5.06	45.8	100	33	37
Pyodermas	20	0.29	75	188	13.2	4.56	40.7	89	30	33
Acne vulgaris	18	0.60	82	295	14.0	4.74	41.9	86	29	34
Seborrheic dermatitis	14	0.40	89	264	13.4	4.39	39.3	89	30	34
Lupus erythematosus (chronic discoid)	10	0.36	87	242	12.8	4.36	38.0	86	29	33
Lupus erythematosus disseminatus	3	0.23	79	161	10.2	3.63	31.1	84	27	33
Dermatitis medicamentosa	9	0.37	72	177	12.2	4.12	36.0	88	28	33
Erythema multiforme	8	0.45	91	269	13.4	4.41	39.8	89	30	33
Exfoliative dermatitis (arsenical)	8	0.41	80	258	12.8	4.45	37.9	84	28	33
Urticaria	6	0.23	85	214	14.5	4.92	43.2	87	29	33
Ichthyosis	5	0.58	81	234	13.1	4.14	39.2	96	32	33
Epithelioma	4	0.32	81	186	13.2	4.49	39.2	87	29	34
Scleroderma	4	0.50	79	268	13.1	4.46	39.3	87	29	33

\* Untreated

† In terms of U S P units of vitamin A

In table 2 the mean plasma levels of ascorbic acid are given for each of the dermatoses diagnosed in 3 or more patients. Significant variations from the mean of the group as a whole were shown by patients with urticaria, lupus erythematosus disseminatus and the pyodermas, these groups having the lowest levels found (0.23, 0.23 and 0.29 mg per hundred cubic centimeters). The highest mean level of ascorbic acid occurred in the 18 patients with acne vulgaris, who averaged 0.60 mg per hundred cubic centimeters of plasma. This high level is possibly explained by the fact that they were largely young, healthy persons receiving a large amount of foods rich in vitamin C. Other dermatoses show mean levels of ascorbic acid scattered

levels of vitamin A are fairly good (84 to 92 U S P units per hundred cubic centimeters), show no decided seasonal fluctuations and compare favorably with those of groups surveyed at their homes in this region.<sup>3</sup> The carotene levels were likewise those customarily found in survey groups.

In table 2 mean plasma levels of vitamin A are seen to range from 56 to 94 U S P units per hundred cubic centimeters, the lowest figures being those for patients with primary and secondary syphilis, dermatitis medicamentosa and pyoderma. The four groups with highest,

3 Milam, D. F. A Nutritional Survey of a Small North Carolina Community, *Am J Pub Health* 32:406-412 (April) 1942.

plasma levels of vitamin A are those with syphilis of the central nervous system, dermatophytosis, erythema multiforme and psoriasis. The carotene levels range from 161 to 295 U S P units of vitamin A per hundred cubic centimeters, with the group having lupus erythematosus disseminatus showing the lowest and the group with acne vulgaris demonstrating the highest level.

It is interesting to note that 22 patients with psoriasis had relatively high vitamin A levels and low carotene values. The only other noticeably disproportionate ratios between vitamin A and carotene were found for 8 patients with generalized exfoliative erythroderma due to arsenical therapy. Their levels of vitamin A were consistently low, and yet the carotene levels were relatively higher than those of other groups. The possibility of hepatic injury might well be considered as contributory to the presence of a low level of vitamin A in association with adequate carotene values. The levels of vitamin A were in most instances higher in males than in females throughout the various groups of dermatoses. Food preferences could explain these differences readily. Carotene levels were higher in women than in men. No explanation is offered here regarding this phenomenon.

**Hemoglobin**—Mean levels approximated 14 Gm for all groups of white patients, being lowest (10.2 Gm) for those with lupus erythematosus disseminatus and highest (15.4 Gm) for those with psoriasis. In 33 white patients with syphilis in different stages the hemoglobin was 13.8 Gm, in 19 Negro patients similarly affected it was 11.1 Gm. This difference in hemoglobin content between the races is slightly greater than that usually found in field surveys. The means are not indicative of the large ranges represented. Almost all the levels below 10 Gm per hundred cubic centimeters were found in women.

**Red Blood Cells**—Counts are approximately 4,500,000 as the mean for all diseases here reported. There is no seasonal variation in mean levels for the group as a whole.

#### COMMENT

Only a few specific groups are selected for comment. In syphilis the mean levels of ascorbic acid for white and for Negro patients averaged 0.4 mg per hundred cubic centimeters for the entire group of 50 patients. Twenty-five patients showed levels under 0.3 mg per hundred cubic centimeters, and 7 of these had zero levels. The possible relationship of levels of ascorbic acid to reactions to treatment at once comes to mind. Except for early infectious syphilis, mean levels of vitamin A were 80 to 94 U S P units, a very satisfactory figure.

Ichthyosis has been described by some as a disease caused by a deficiency of vitamin A, but in the 5 patients studied only normal plasma levels of vitamin A were found.

In a comparison of 28 patients with dermatophytosis and 16 patients with dermatophytoid and dermatophytid all the determinations were essentially normal, and the mean figures were remarkably similar. From this one would conclude that none of the findings represented any etiologic or even contributory factors in the production of the dermatophytid. In a like manner there were no distinguishing differences in comparing the findings for 10 patients with stasis dermatitis and 24 patients with stasis dermatitis plus a generalized bacterid.

In 18 patients with acne there was no inadequacy in ascorbic acid, vitamin A or carotene, and judging by these findings there is no indication for treatment with these vitamins for patients in this region afflicted with acne.

The group with the pyodermas studied (furunculosis, impetigo, sycosis vulgaris and cellulitis) was significantly low in vitamins A and C and administration of vitamins seems justifiable in these diseases. It is possible that in pyogenic infections the stores of vitamins are more readily exhausted than in other dermatoses.

As can be seen from table 2, the group with scleroderma (4 patients) and those with exfoliative dermatitis (8 patients) had low levels of vitamin A and high levels of carotene. If this disproportion were due to disturbed hepatic function in converting carotene to vitamin A, administration of vitamin A to these patients would be justified.

It appears that the nutritional status of these patients in the dermatologic clinic closely parallels that of inhabitants of the rural communities already surveyed in this state.<sup>4</sup> The nutritional status of this group of 354 patients seems to be representative of the milieu from which they come, but no special nutritional condition can be singled out as a factor in their dermatologic lesions. Whether this same incidence of diseases of the skin would occur in this same population if it were on a higher nutritional level is a matter the data do not cover. The conclusion seems warranted, however, that the cutaneous diseases here listed do not have vitamin A or C deficiencies as an important etiologic or predisposing agent, since the plasma levels of the patients were scattered throughout the range.

<sup>4</sup> Milam, D. F., and Anderson, R. K. A Nutritional Survey of an Entire Rural County in North Carolina, South. *M. J.* 37: 597-605 (Nov.) 1944.

of the plasma levels of these nutrients. Individual variations in minimum requirement could theoretically be a factor of importance. It seems probable to us that such effect as diet might have on these cutaneous abnormalities would be in increasing the severity of the disease rather than in serving as a precipitating cause. This would certainly be true of the diseases of specific known cause. The relation of diet and dermatoses of unknown cause is not clear, and unfortunately no light is shed on that point by the data here included.

#### SUMMARY AND CONCLUSIONS

In a period of nine months 354 unselected dermatologic patients were given a nutritional survey including a careful history of food intake and a laboratory study of vitamins, hemoglobin and erythrocytes in the blood. The findings both as to food intake and as to blood levels were typical of the usual findings in field nutritional surveys in North Carolina. It is concluded that the nutritional status was not a factor in the precipitation of the dermatologic diseases of the patients studied.



## Clinical Notes

### PENICILLIN OINTMENT FOR PYODERMAS

HAROLD M. JOHNSON, M.D., HONOLULU, TERRITORY OF HAWAII

I have been interested in the potential use of penicillin as a dermatologic bacterial inhibitor for the last twelve months<sup>1</sup>. Recently I have used penicillin purified in a water-miscible oycholesterol-petrolatum base<sup>2</sup> with such success that I believe a note on its use and preparation is warranted.

Twenty-five cases, including cases of impetigo contagiosa, infectious eczematoid dermatitis, dermatitis repens, furunculosis, interdigital pyoderma of the feet, lymphangitis (localized), sycosis vulgaris and acne necrotica, were studied. The impetiginous crusts were left intact, and debridement was done to the pyodermic lesions three to five days after the initial visit.

For several months I have been collecting "empty" penicillin bottles used at Queens hospital. They had contained 100,000 units of penicillin per bottle, which had been diluted with sterile isotonic solution of sodium chloride to give 10,000 units per cubic centimeter. The "empty" bottles previously were thrown away by the hospital supply department. I made daily rounds of the wards to gather them, and then I stored them in

the refrigerator until used. Each bottle contained from 0.25 to 2 cc of penicillin, which was removed with a hypodermic syringe. One cubic centimeter of penicillin was placed in a sterile ointment jar, and 2 ounces (60 Gm) of the base (sterile) was gradually added and thoroughly mixed. Thus each gram of ointment contained roughly 166 units of penicillin.

The jars of ointment were then kept in refrigeration until used. Each patient was advised to employ sterile technic and refrigeration when using the ointment. I have used penicillin ointment six to eight weeks old and found it to be effective.

Penicillin ointment was effective in treatment of the aforementioned pyodermas. I was impressed with its efficacy in a case of stubborn chronic sycosis vulgaris which had resisted all the commonly used sulfonamide compounds, roentgen therapy and vaccines. Pruritus stopped in twenty-four hours, and the eruption cleared in two weeks. The other infections cleared in five to ten days. No intolerance or sensitization was noted.

Schoch<sup>3</sup> recently used washings of emptied penicillin ampules and was enthusiastic as to their use. The rapid bacteriostatic action places the ointment in a unique position as a valuable adjunct to the dermatologic therapeutic armamentarium.

1 Johnson, H. M. Penicillin Therapy of Impetigo Contagiosa and Allied Diseases. Use of Penicillin Inoculated Dressing, Arch. Dermat. & Syph. 50 1-5 (July) 1944.

2 The preparation used was Aquaphor.

3 Schoch, A. G. Local Penicillin Therapy, Arch. Dermat. & Syph. 50 202 (Sept) 1944.

# Abstracts from Current Literature

EDITED BY DR HERBERT RATTNER

CAPILLARY PERMEABILITY IN MYXEDEMA KURT LANGE,  
Am J M Sc 208 5 (July) 1944

Attempts of previous observers have failed to establish the mechanism of the interstitial edema and serous effusions in myxedema Utilizing a photoelectric skin colorimeter after injection of fluorescein, Lange demonstrated a decided increase in capillary permeability in 5 cases of myxedema With thyroid therapy the permeability rapidly returned to normal

DIABETES MELLITUS ASSOCIATED WITH ALBRIGHT'S SYNDROME (OSTEITIS FIBROSA DISSEMINATA, AREAS OF SKIN PIGMENTATION, AND ENDOCRINE DYSFUNCTION WITH PRECOCIOUS PUBERTY IN FEMALES) FRANKLIN B PECK and CHARLES V SAGE, Am J M Sc 208:35 (July) 1944

To the growing list of reported cases of Albright's syndrome Peck and Sage add another, the first known case of its association with diabetes Study of the diabetes suggested the presence of a complex endocrine disturbance, possibly originating before birth, and implicating the pituitary gland

SCLERODERMA HEART DISEASE SOMA WEISS, EUGENE A STEAD JR, JAMES V WARREN and ORVILLE T BAILEY, Arch Int Med 71 749 (June) 1943

Weiss and his associates call attention to a form of heart disease associated with scleroderma They state that cardiac symptoms have rarely been described in the course of scleroderma, although pathologic changes have been reported in a few cases They record data from 9 cases in which patients presented signs and symptoms suggesting heart failure accompanied by the classic picture of scleroderma In 6 instances the outcome was fatal, and autopsy was performed in 2 cases, at which myocardial scarring of a peculiar nature was observed (histologic details are given) The authors believe that scleroderma heart disease is a clinical and pathologic entity

ALLERGY FRANCIS M RACKEMANN, Arch Int Med 73 248 (March) 1944

In a review of the literature on allergy Rackemann calls attention to a number of articles on industrial dermatitis, contact dermatitis from other causes, drug allergy and atopic eczema

INFECTIOUS MONONUCLEOSIS ANDREW W CONTRATTO, Arch Int Med 73 449 (June) 1944

In the course of a review of 196 cases of infectious mononucleosis Contratto discusses the eruption characteristic of that disease He observed such an eruption in only 10 cases, and he points out its frequent confusion with eruptions due to toxemia or drugs or with entirely coincidental eruptions The characteristic eruption closely resembled that of mild German measles, was morbilliform and transient and did not last over forty-eight hours Contratto does not feel that it is charac-

teristic enough in itself to be relied on as a diagnostic feature

TREATMENT OF SCARLET FEVER MAX J FOX and N F GORDON, Arch Int Med 74 1 (July) 1944

Fox and Gordon review the therapeutic results in scarlet fever in two series of 1,000 cases each They conclude that sulfonamide compounds find their chief value in the treatment of certain complications but are of no value in the management of the toxic phase or type of scarlet fever The use of commercial antitoxin combats the toxic phase of the disease but introduces the danger of foreign protein reactions Pooled human convalescent serum produced rapid clinical response when administered to patients with scarlet fever and offers the best means of therapy

A MIXED TUMOR OF THE SALIVARY GLAND TYPE ON THE LEFT HAND BENJAMIN HIGHMAN, Arch Path 37:387 (June) 1944

Since mixed tumors of the salivary gland type occurring elsewhere than on the head and neck have rarely been reported, Highman describes such a tumor occurring on the hand Trauma is suggested as a possible predisposing factor The view is advanced that these tumors are essentially epithelial in origin, possibly derived from sweat glands, and that the stromal portions, particularly the cartilaginous and myxomatous tissues, are epithelial products In some areas of the tumor the author thought he observed gradual transitions from compact epithelial masses to loose myxomatous tissue and from typical epithelial cells to chondrocytes

MELANOCARCINOMA OF THE CERVIX UTERI OR VAGINAL VAULT CARL E TAYLOR and HOWARD K TUTTLE, Arch Path 38 60 (July) 1944

Because of the rarity with which malignant melanomas develop primarily in tissues other than the skin and retina, Taylor and Tuttle describe an instance in which such a tumor arose on the anterior lip of the cervix or possibly in the vaginal vault immediately adjacent to the cervix so that the tumor could present at the cervix The patient had a postoperative survival period of thirteen years, with multiple local recurrences, and finally died with general metastases

THERAPEUTIC VALUE OF GRENZ RAYS IN DERMATOLOGY SAMUEL M BLUEFARB, Arch Phys Therapy 25 400 (July) 1944

Bluefarb reports on the use of grenz rays and states that it is his belief that whatever failures have occurred in grenz ray therapy have been due to excessive dosage He obtained good results with fractional treatment, the interval between doses varying from one week when 60 to 120 r was given per treatment to three weeks when 300 to 600 r was given and six to eight weeks when doses of 1,000 r or more were given

He found grenz rays safer and superior to roentgen rays in the treatment of the following diseases of the

skin (1) nevus flammeus, (2) dermatitis of the external auditory canal, (3) lichen chronicus simplex and (4) scrotal and penile dermatitis. For certain other diseases he continued to use grenz ray therapy after the maximum amount of roentgen radiation had been given. The recommended dosage is listed for various dermatoses.

LYNCH, St Paul

TREATMENT AND PREVENTION OF DERMATOPHYTOSIS AND RELATED CONDITIONS. JOSEPH G. HOPKINS, ARTHUR B. HILLEGAS, EARL CAMP, R. BRUCE LEDIN and GERBERT REBELL, Bull U S Army M Dept, June 1944, no 77, p 42

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the office of Scientific Research and Development of the National Research Council and Columbia University. The findings, which should not be considered final, are stated somewhat categorically for the sake of brevity.

Inflammation of the skin of the feet may result from many causes, of which the following were recognized by these authors: mycotic infection, pyogenic infection, allergy, hyperhidrosis, trauma and hypostasis.

The authors stress two principles of treatment: (1) hygienic measures, such as cleanliness, dryness and aeration of the areas involved and elevation of the feet to relieve hypostatic congestion, and (2) active treatment as such, which must avoid injury and vary with the causation and type of involvement.

Fungi have been found in about 70 per cent of cases of intertrigo of the toes and in over 90 per cent of dyshidrotic lesions on the soles. The most effective treatment agents in such cases are those which attack the fungi. In general, iodine, a number of mercurials, thymol, and several essential oils have seemed low in effectiveness and irritating in a significant number of cases. The dyes, too, appeared weakly fungicidal according to these investigators. Of the familiar fungicides, benzoic acid, salicylic acid and sulfur were the most useful drugs. Ointments should be used only at night and wiped off thoroughly in the morning and a powder applied to the toes. The addition of 10 to 25 per cent bentonite to talc powder increases its absorptive quality.

In cases of a simple intertrigo, an ointment or paint should be applied to the sides and webs of all the toes and the entire sole every night until the skin appears normal and should also be applied once a week throughout the warm season, to prevent relapse. A benzoic acid paint is recommended among others, the formula for which is benzoic acid 5 Gm, acetone 15 cc and cottonseed oil 85 cc. For obstinate infections sulfur and salicylic acid ointments are recommended. For fissured and denuded areas an ointment of zephiran chloride (zephiran chloride [10 per cent] 5 cc, water 20 cc, hydrous wool fat 25 cc and petrolatum 50 cc) was very useful. For some obstinate infections, 5 per cent sulfathiazole ointment succeeded when zephiran ointment failed to bring improvement. Potassium permanganate baths are recommended (about 1:4,000) for acute or overtreated dermatoses with dyshidrotic lesions on the soles. Zephiran (20 cc of 10 per cent concentration of zephiran chloride) in 2 liters of water proved to be a very effective nonirritating foot bath.

The follow-up treatment after the active lesions have subsided is stressed and consists of hygienic measures and fungicidal paints.

Onychomycosis was treated by thorough removal of all portions of the nail that had become friable or

loosened from the bed, and a chrysarobin paste was used among others. A satisfactory paint for lesions of the groin and trunk that are not eczematized is recommended. It consists of salicylic acid 3 Gm and tincture of merthiolate (1:1,000) 100 cc.

The authors discuss at length the symptoms and treatment of local hyperhidrosis and stress the importance of prophylaxis. There are numerous formulas in this paper which cannot be given here on account of space. Physicians who know how difficult it is at times to treat dermatophytosis will appreciate the excellent report.

TRENCH FOOT. ROBERT C. BERSON and RALPH J. ANGELUCCI, Bull U S Army M Dept, June 1944, no 77, p 91

The critical temperature for cooling tissues according to Berson and Angelucci appears to be in the region of  $-5$  to  $-7$ . Tissues cooled below this temperature are killed.

The term "frostbite" should be reserved for the condition in which tissues have been cooled below the critical temperature, while the term "trench foot" should be reserved for feet which show evidence of damage due to cooling above the critical temperature, according to these authors.

In the 144 cases of trench foot studied by Berson and Angelucci there was presumptive evidence that a past history of symptoms from exposure, a family history of diabetes and hypertension and a past history of smoking were not important predisposing factors.

A series of 88 consecutive patients was divided into three treatment groups. The first group was given a regular hospital diet, absolute rest in bed and as much codeine as required to keep them fairly comfortable. The second group was in addition given Buerger's exercises four times daily. The third group was given no exercise but was given 50 mg of thiamine hydrochloride hypodermically twice daily. There was no demonstrable significant difference in the comfort, the amount of sedation required or the rate of recovery in the three groups.

The following suggestions for early treatment were given: 1. Removal of all potentially constricting clothing and shoes. 2. Prohibition of walking or weight bearing on the feet. 3. Immediate application of cooling by the most efficient method at hand and continuation of such cooling until its slow withdrawal does not cause the feet to become noticeably warmer than the rest of the body. 4. Strict avoidance of all warming agents (clothing, dressing hot water bottles, stoves, etc). 5. Strict prohibition of all massage. 6. Avoidance of sympathetic block at the early stage.

STRAKOSCH, Denver

THE EFFECT OF STILBESTROL ON EXPERIMENTAL STREPTOCOCCAL INFECTION IN MICE. G. E. FOLEY and W. L. AYCOCK, Endocrinology 35:139 (Sept.) 1944

Foley and Aycock cite a number of studies in recent years which draw attention to the importance of such factors as heredity, nutrition and endocrine function in the susceptibility and resistance to disease. They report an experiment which illustrates the importance of host rather than parasite after exposure to an infectious agent. A single dose of diethylstilbestrol rendered mice highly resistant to a dose of mouse-virulent hemolytic streptococci which regularly killed normal control mice of the same age and sex.

LYNCH, St Paul

PENICILLIN TREATMENT OF EARLY SYPHILIS J F MAHONEY, R C ARNOLD, BURTON L STERNER, AD HARRIS and M R ZWALLY, J A M A 126 63 (Sept 9) 1944

The authors have treated approximately 100 patients with early syphilis. Therapy consisted of an intramuscular injection of 20,000 units of penicillin administered at three hour intervals for sixty injections. The total amount of penicillin employed was 1,200,000 units. No other antisyphilitic medication was used.

Herxheimer-like reactions, or therapeutic shock, of varying degrees of severity were observed during the first day of treatment in 86 patients. Fifty-two patients were observed for a minimum of seventy-five days after treatment. For 7 of these patients treatment resulted in failure.

Primary syphilis responded more favorably than secondary syphilis. When penicillin is used in therapy of syphilis, a certain proportion of patients fail to experience the same curative response demonstrable in the majority of patients.

THE TREATMENT OF EARLY SYPHILIS WITH PENICILLIN JOSEPH E MOORE, J F MAHONEY, WALTER H SCHWARTZ, THOMAS H STERNBERG and W B WOOD, J A M A 126 67 (Sept 9) 1944

When the books of the Penicillin Panel of the Subcommittee on Venereal Diseases of the National Research Council were temporarily closed as of May 25, 1944, 1,587 case reports of early syphilis treated with penicillin had been received, of which 1,418 were suitable for analysis. In the majority of the cases the patients were observed for less than two months.

The incidence of relapse when penicillin was administered alone was in direct relationship to the total dosage given by the intramuscular route in a seven and one-half day period, greatest with 60,000 units and least with 1,200,000 units. Relapse appears to be more frequent after intravenous than after intramuscular administration of comparable doses. Penicillin has a favorable effect on early asymptomatic neurosyphilis, acute syphilitic meningitis, early syphilis resistant to treatment with arsenic and with bismuth preparations and infantile congenital syphilis. Herxheimer reactions after use of penicillin in treatment of early syphilis were frequent but not serious. The minimum dose, especially for secondary syphilis, should not be less than 1,200,000 units, probably it should be more.

Ninety-four patients who were given 60,000 or 300,000 units of penicillin and 320 mg of mapharsen in eight days were followed for thirty-eight days or more. Only 1 relapse occurred.

THE ACTION OF PENICILLIN IN LATE SYPHILIS JOHN H STOKES, T H STERNBERG, WALTER H SCHWARTZ, JOHN F MAHONEY, J E MOORE and W BARRY WOOD, J A M A 126 73 (Sept 9) 1944

One hundred and eighty-two patients with late syphilis, preponderantly neurosyphilis (122 cases), were treated with penicillin therapy and were under observation from eight to two hundred and fourteen days after treatment.

The lesions of benign gummatous syphilis healed with a dosage of approximately 300,000 units in twelve to forty-six days. Penicillin produced a reduction of titer of syphilitic reagin in the blood in from 50 to 60 per cent of patients with late syphilis. The abnormal spinal fluid was improved to some degree in 74 per cent and definitely in 33 per cent of patients with neurosyphilis.

In patients with late congenital syphilis, penicillin produced rather equivocal though at times dramatically favorable results on interstitial keratitis. In 2 cases optic neuritis improved. In 2 cases results on eighth nerve deafness were equivocal. Neurogenic arthropathy (Charcot joint) was unaffected.

Therapeutic shock (Herxheimer) effects occur, may be serious and should be guarded against by reduced dosage during the first twenty-four to forty-eight hours.

HENSCHEL, Denver

THE VALUE OF THE PATCH TEST IN POISON IVY DERMATITIS, WITH CONSIDERATION OF GROUP REACTIONS BETWEEN RHUS EXTRACT AND TURPENTINE, PYRETHRUM, RAGWEED OIL AND 3-GERANYL CATECHOL HARRY KEIL, J Allergy 15 259 (July) 1944

The results of studies in 72 cases of dermatitis venenata of various origins, mainly plants, lead the author to support the following generally accepted opinions on the uses and limitations of the patch test in relation to poison ivy dermatitis. (a) A positive result of a patch test with rhus extract is not of itself diagnostic but simply indicates sensitization to the plant, past or present. Greater diagnostic significance can be attributed to a positive reaction in children below the school age. (b) A negative result eliminates past and present hypersensitiveness to Rhus toxicodendron, on this point rests the chief value of the test in differential diagnosis of poison ivy dermatitis.

The author submits evidence to show that there is no apparent biologic relation between hypersensitiveness to poison ivy and that to fresh turpentine of various types or to  $\alpha$  and  $\beta$  pinene. Group reactions may be encountered with old specimens of turpentine, but this may be due to an increase in the phenolic portion of turpentine.

He did not find a group relation between the active ingredient of poison ivy and pyrethrum or ragweed oil. However, he found that 3-geranyl catechol is biologically related to the active principle in poison ivy.

PENICILLIN ALLERGY ON THE PROBABILITY OF ALLERGIC REACTIONS IN FUNGUS-SENSITIVE INDIVIDUALS SAMUEL M FEINBERG, J Allergy 15 271 (July) 1944

In a previous report, the author showed that penicillium spores constitute 11 per cent of the fungus spore content of the air in midwestern United States and that approximately 6 per cent of allergic persons are sensitive to the antigen of the penicillium family. He further demonstrated that persons sensitive to one species of Penicillium will react to other species of the same genus.

In the present study, the author attempted to determine whether sensitivity to Penicillium would induce allergic reactions to penicillin.

Ten patients who were clinically mold-sensitive and who gave positive reactions to scratch tests with extracts of various species of penicillium, including Penicillium rubrum, Penicillium digitatum and Penicillium notatum were found to give negative reactions to scratch tests with solid penicillin and freshly prepared solution containing 5,000 units per cubic centimeter. Intracutaneous tests with 5, 50 and 500 units per cubic centimeter also elicited negative reactions.

Further study revealed that intracutaneous tests with a preparation of greater purity containing 25,000 units of penicillin per cubic centimeter elicited a negative reaction in a number of Penicillium-sensitive persons and control subjects. From these observations the

author believes that the purer preparation could be tolerated by a *Penicillium*-sensitive patient in doses of at least 500,000 units

MENDELSON, New York

#### EXPERIMENTS ON SCABIES PROPHYLAXIS KENNETH MELLANBY, Brit M J 1 689 (May 20) 1944

A prophylactic method for scabies should be safe, efficient, simple and cheap. An experiment was made with a standard sheep dip, which failed to kill 50 per cent of the mites and was hence discarded as unsatisfactory.

The author expresses the opinion that universal dipping with benzyl benzoate emulsion would prove completely successful in wiping out scabies. In 1 experiment on these lines, 804 patients in a hospital where scabies was a major problem were given a single treatment with the emulsion. Since that date scabies has given no further trouble.

In another experiment children were treated prophylactically by rubbing 1 cc of benzyl benzoate on the hands and wrists only every two weeks for twelve treatments. The incidence of scabies was significantly greater in a control group than in a treated group. Mellanby concludes, after experiments necessitating a quarter of a million inspections of school children, that scabies prophylaxis is not practicable apart from the normal treatment of the disease.

Frequent examination by trained personnel and institution of treatment for persons known to have the disease and for all contacts can rapidly reduce the incidence of scabies.

#### CONTROL OF CRAB LICE KENNETH MELLANBY, Brit M J 1 720 (May 27) 1944

'Lethane 384 special' and 'technical lauryl thiocyanate' (a commercial product and not a pure substance) have been used against head lice and are lethal to crab lice. The former substance is rather irritating, causing discomfort when applied to the genitals, hence it is not suitable for use against crab lice. The latter in emulsion form caused little discomfort and was effective. One application only was given, less than 10 cc of the emulsion being used. No relapses occurred in 177 cases in which it was used.

The formula is as follows: "technical lauryl thiocyanate," 50 cc, lanette wax SX, 20 Gm, water, 950 cc. The lanette wax was melted on a water bath, the lauryl thiocyanate added and the mixture heated to a temperature of between 60 and 70 C. The mixture was poured into the water, previously heated to the same temperature, and stirred until cold.

[Lanette wax SX is a cream-colored wax with a melting point of approximately 50 C and said to be a sulfated cetyl-stearyl alcohol. It is self emulsifiable with water, producing a neutral emulsion of the oil in water type. The wax will also emulsify many thick oils, fats and waxes, with each case giving an oil in water emulsion. Supplies of the wax are strictly controlled and are limited.]

#### CONTROL OF SCABIES BY USE OF SOAP IMPREGNATED WITH TETMOSOL R M GORDON, T H DAVEY, K UNSWORTH, F F HELLIER, S C PARRY and J R B ALEXANDER, Brit M J 1 803 (June 17) 1944

Tetraethylthiuram monosulfide (tetmosol) when combined with soap in 5, 10 and 20 per cent dilutions has

been shown to retain its sarcopticidal properties. Tetmosol soap was shown to have a local therapeutic effect in cases of rat scabies.

Six men with scabies receiving five to six baths with 20 per cent tetmosol soap on successive days were all cured. Of a further series of 110 men receiving three baths with 20 per cent tetmosol soap over a period of a week, 80 per cent were cured.

The simplicity of a procedure involving bathing with a soap tablet suggests its possible value in communities disorganized as a result of war and in which it is not practicable to employ standard methods of treatment.

In the small number of persons treated, the incidence of dermatitis following the use of the soap for short periods was low.

#### VARICELLA AND HERPES ZOSTER AN EXPERIMENT J R M WHIGHAM and D B HANDELMAN, Brit M J 1 812 (June 17) 1944

In view of the suggested relationship between the etiologic agents of varicella and herpes zoster, an experiment was carried out to find whether convalescent zoster serum would be effective in preventing varicella in persons in contact with varicella.

Blood was taken from 2 patients with herpes zoster during the second week after appearance of the eruption. After clotting, the serum was stored at 4 C till used (two months). On the appearance of a case of varicella in one of the children's wards, 7 patients were given an intramuscular injection of 20 cc of the serum on the day after the case of varicella appeared, 6 others were used as controls. None of the 13 had a previous history of varicella. Six of the 7 treated patients remained free of the disease, 1 had only nine lesions. Five of the 6 untreated children contracted varicella, having from 63 to 108 lesions.

#### PENICILLIN IN SKIN DISEASE I A ROXBURGH, RONALD V CHRISTIE and A C ROXBURGH, Brit M J 2 524 (July 25) 1944

The present survey comprises 75 cases, all of which were investigated bacteriologically before treatment was begun.

Of 15 patients who had had sycosis barbae for a long time, 5 were initially cured and remained cured for periods up to nineteen weeks. Three patients, though initially cured, had relapses after periods varying from ten days to five weeks, they were again cured after the relapse and these cures lasted from nine to twenty-two weeks. Five patients initially cured had relapses after periods varying from a few days to fifteen weeks, and their relapses remained uncured. One patient was never cured, and treatment of another was still in progress at the time of writing.

Penicillin was usually applied in an ointment containing 400 units of calcium or sodium penicillin per gram of base, the latter being a mixture of equal parts of lanette wax SX, petrolatum and water. In other cases solutions of penicillin (1,000 units of the calcium salt per cubic centimeter) were used. The use of penicillin in solution is not recommended except when the ointment has caused irritation, as it tends to be extravagant of penicillin and does not appear to produce final cure any more quickly than the ointment, even though there is a more dramatic response during the first few days. Treatment should in all cases be continued for a few days after apparent cure.

In 11 of 12 cases impetigo was cured in an average of eight or nine days. Individual lesions healed in

about four days. One application of the ointment a day was as effective as two. In 9 cases of chronic eczema with a secondary infection it was indicated that penicillin ointment is worthy of trial in such cases. In 8 cases of blepharitis the initial response was encouraging, although relapses were frequent. In 7 cases of external otitis with mixed flora incomplete cure and early relapses were the rule. In 5 cases boils were treated with the ointment, with indications that penicillin may be useful in stopping a series of recurrent boils, however, penicillin applied externally appeared to have no effect whatever on the evolution of an individual boil. Penicillin ointment was of little value in 2 cases of pustular acne, but the solution was beneficial when sprayed on in a case of acne conglobata. It is suggested that the solution may be of more value, though more extravagant, than the ointment in the treatment of acne and that the response will depend on the extent to which staphylococci are accountable for the suppuration in each case.

Two patients with generalized seborrheic dermatitis were treated, 1 patient failed to respond to ointment but recovered temporarily when solution was sprayed on the affected areas, the other responded to ointment only in areas where secondary infection was great. In a third patient, the disease, which was confined to the scalp, cleared up well when treated with ointment (a secondary staphylococcal infection was present). One small carbuncle, which was discharging, healed in twelve days under treatment with ointment. A patient who had Bockhart's impetigo accompanied by boils improved, but the boils were hardly affected. A patient with dermatitis repens (Crocker) failed to respond. Four patients with chronic ulceration of the lower limb of uncertain causation all improved. Two patients with varicose ulceration were treated, 1 patient failed to respond, and the other, who had varicose eczema as well, was greatly benefited. One patient with psoriasis, 1 with herpes labialis and 1 with pemphigus vulgaris were unaffected.

SHAW, Chattanooga, Tenn



# Society Transactions

## MINNESOTA DERMATOLOGICAL SOCIETY

S E SWEITZER, M D, *President*

H A CUMMING, M D, *Secretary*

*Minneapolis, Feb 4, 1944*

**A Case for Diagnosis (Purpura Annularis Telangiectodes?)** Presented by DR S E SWEITZER, Minneapolis

A D, a 70 year old white man, was admitted to the Minneapolis General Hospital on Jan 11, 1944, complaining of ringlike red spots on the right leg and in the axillas of about two weeks' duration. The lesions began as small rings on the thighs, increased in number and in size and spread to the chest. They did not itch, nor were they painful. The lesions when first seen varied from plaques 1 cm in diameter to rings about 4 cm in diameter. These did not blanch on diascopy. The patient had severe stasis dermatitis and resultant scarring and large varices. One lesion on the medial portion of the right thigh was blanched with ethyl chloride, and after the resultant erythema subsided it was gone.

Serologic reactions for syphilis were negative. Repeated smears and cultures were negative for fungi.

Examination shows an elderly man presenting an irregular ring composed of tiny brownish red papules with light scales on the periphery. The center of each lesion is clear. (Microscopic sections were shown.)

### DISCUSSION

DR HAMILTON MONTGOMERY, Rochester. I do not believe that this eruption is purpura annularis telangiectodes. The sections show extravasation of red blood cells beneath the epidermis but no evidence of iron pigmentation with the ordinary stains, no special stains being shown. I favor a diagnosis of an erythema multiforme type of reaction.

**Parapsoriasis** Presented by DR CARL W LAYMON, Minneapolis

Miss M H, a white woman aged 35, noted an eruption on the chest in the spring of 1943. This eruption spread over the entire trunk, arms and thighs.

Examination showed erythematous squamous patches on the thighs, trunk and arms.

The Kline and Wassermann reactions were negative.

### DISCUSSION

DR C W LAYMON, Minneapolis. When this patient was first seen, the lesion looked like pityriasis rosea. Histologic section was diagnosed as pityriasis rosea. She has had the eruption about one year, and it has not changed under treatment.

DR S E SWEITZER, Minneapolis. With what has she been treated?

DR C W LAYMON, Minneapolis. At present she is getting ultraviolet radiation and 20 per cent sulfur ointment, with some improvement from treatment in about three weeks. Pityriasis rosea should not take that long to improve and should respond better to treatment.

DR R J BURKHART, Rochester (by invitation). I think the eruption is consistent with parapsoriasis clinically and histologically. Parapsoriasis may improve under treatment, and in some cases it clears up completely and does not recur, however, this is not the rule. Have you tried intramuscular injections of typhoid vaccine in treatment of pityriasis rosea?

DR S E SWEITZER, Minneapolis. No.

DR R J BURKHART, Rochester (by invitation). My colleagues and I have tried it on 2 patients and we did not think either of them showed any symptomatic or clinical improvement.

**Lichen Sclerosus et Atrophicus** Presented by DR CARL W LAYMON, Minneapolis

E B, a white woman aged 59, had noticed itching of the vulva for four years. A roentgenologist gave her about 800 r of roentgen radiation in two treatments in September 1941.

Examination showed sclerotic white patches involving the entire vulva. The labia minora are shrunken. There is a plaque of lichen sclerosus et atrophicus on the right thigh near the groin.

### DISCUSSION

DR C W LAYMON, Minneapolis. I thought there were typical lesions of lichen sclerosus in the groin. There was atrophy of the labia majora but not particularly of the labia minora, and I do not think that there was any evidence of true kraurosis. In my opinion the picture fits in perfectly with the picture of lichen sclerosus et atrophicus.

DR STEPHEN EPSTEIN, Marshfield, Wis. I should like to ask Dr Laymon how the eruption responds to treatment with estrogen.

DR C W LAYMON, Minneapolis. This particular patient received no estrogenic substance, but I think it is the experience of most physicians that this disease does not respond to estrogen.

DR HAMILTON MONTGOMERY, Rochester. I agree with Dr Laymon.

**Calcinosis Cutis** Presented by DR E MICHELSON, Minneapolis and (by invitation) DR K B SKUBI, Minneapolis

H T, a white woman aged 36, first noted swelling of her lower extremities, weakness and dyspnea in March 1943. The swelling persisted, the weakness and dyspnea increased, and anorexia and nausea were often distressing. Hardness of the swollen extremities, first noted by the patient in August 1943, became increasingly prominent. A few weeks before her admission to the University Hospital, Dec 3, 1943, swelling of the eyelids and lesions under the breasts appeared. The past history revealed frequency of urination for many years. Amenorrhea had always been present. Subsequent to her admission, the diagnosis of chronic glomerular nephritis was made by renal biopsy.

Laboratory observations of interest were (1) pronounced and continued albuminuria, (2) continued retention of nitrogenous waste products, (3) profound anemia, (4) low blood cholesterol, with values of 80 and 90 on two determinations, (5) blood calcium level

of 92, with phosphorus 82 and (6) severe acidosis as manifested by several values for carbon dioxide-combining power between 20 and 30. Aspiration of sternal marrow showed erythroid hyperplasia to be the predominant feature. Roentgenologic studies showed remarkable calcification in the soft tissues of the right thigh, calcification of pelvic vessels was also noted.

After supportive therapy, including transfusions of blood, the edema subsided and there was decided improvement in the patient's general condition. The appearance of the skin in the areas involved became more striking.

Examination shows a mottled pink macular eruption on the posterior aspect and the sides of the legs and thighs. Palpation here reveals a shotty induration underlying the lesions. The same shotty induration is also palpable on the anterior aspect of both thighs. Pink papules and small nodules, some of which also are shotty and hard to palpation, are present on the lower portion of the breasts. Palpation of the radial arteries reveals hard and beaded vessels. There is considerable cloudiness of the cornea of both eyes.

#### DISCUSSION

DR H E MICHELSON, Minneapolis. Dr Lynch made the diagnosis.

DR F W LYNCH, St Paul. Calcium may be found in the skin in a variety of forms. Osteosis cutis, the formation of true bone in the skin, is an extremely rare condition. In calcinosis cutis the calcium is not of the same structure as bone, it may be localized or generalized in distribution. Localized calcinosis may be associated with vascular disturbance, inflammation or tumors. Generalized calcinosis is usually regarded as of two types. In the metastatic form the calcium is withdrawn from bone and redeposited in the skin and also in other organs and tissues, roentgenologic studies of the skeleton then show osteoporosis, which is not demonstrable in this patient. She has calcinosis cutis of the metabolic form. Little is known as to the cause of this disease, but it is sometimes associated with edema, anemia and renal dysfunction, as noted in this case. In a generalized disturbance like this it is difficult to understand why the skin should show such extensive changes, but Dorrfer has pointed out that in the normal metabolism of calcium the skin serves as a storage depot.

DR K SKUBI, Minneapolis (by invitation). This case probably presents a combination of the dystrophic and the metabolic (or generalized) form of calcinosis. The cutaneous and subcutaneous deposits of calcium probably represent the dystrophic type, whereas the widespread arterial calcification and the possible corneal deposits are manifestations of the generalized form.

In trying to explain the calcification in this case it may be said that in chronic glomerulonephritis the parathyroid glands are frequently hypertrophied at autopsy. It is known, of course, that metastatic calcification is often observed in cases of hyperparathyroidism. The exact explanation for this is not known. Kleinman feels that this type of calcification, or any type of calcinosis, may be due to a combination of several factors, both local and systemic. Inasmuch as this patient does have a chronic glomerulonephritis, she may have had a mild local inflammatory process, which is frequently seen in persons with long-standing edema. This may explain the dystrophic calcification in this particular case. In other words, the mild inflammation or chronic stasis in the edematous extremities may have resulted in an increased alkalinity of the tissues and subsequent

deposition of calcium. Increased local alkalinity is thought to be one of the factors influencing calcium deposition. The generalized form of calcification has been reported in chronic glomerulonephritis in the past. Virchow observed it in several cases as far back as 1855.

#### Dermatomyositis with Scleredema Presented by DR S E SWEITZER, Minneapolis

E L, a white woman aged 22, was admitted to Minneapolis General Hospital on Jan 24, 1944, complaining of vomiting, cough, headache, anorexia, swollen eyelids and joints of three days' duration and painful red areas on the arms, legs and fingers. On examination the patient showed painful annular dusky red nodules about 3 cm in diameter on the nose, ulnar portion of the forearms and elbows and fingers. The eyelids were swollen, and the face assumed a masklike appearance.

Serologic reactions for syphilis were negative. Blood and urine were normal except for sugar (1 plus) in the urine, which has not been found since. On February 1 the hemoglobin content was 86 per cent and the white blood cell count 5,000, with 42 per cent neutrophils, 43 per cent lymphocytes, 13 per cent monocytes and 2 per cent eosinophils.

Examination shows a woman appearing younger than 22, with pain and tenderness in muscles and joints of the legs, arms and pectoral girdle.

#### DISCUSSION

DR L H WINER, Minneapolis. This patient came to the clinic complaining of severe pains, as her history states. There was extreme tenderness of the muscles over the midportion of the various extremities and not at all over the joints of the extremities. The muscles were tender and painful. The appearance of the skin when she first came in was white and waxy. Today it appears waxy, but the whiteness has almost entirely left. Also, the edema which was apparent early has more or less disappeared. However, on microscopic section, we were able to see that the connective tissue was torn and disrupted by infiltration of serous exudate. In areas the subcutaneous muscles show definite perivascular lymphocytic infiltrate as well as nests of fibroblastic proliferation.

DR HAMILTON MONTGOMERY, Rochester. I should hesitate to make a diagnosis of dermatomyositis with scleredema. The history of malaise associated with edema, pain and tenderness of the muscles with an acute onset supports the diagnosis of scleredema. The biopsy specimen of muscle failed to show any infiltrate in the muscles and only slight fibrosis in the connective tissue. The skin showed decided edema between the connective tissue fibers with extravasation of serum or a serous substance, all of which fits in with scleredema. Dr O'Leary has emphasized that in the early edematous phases distinction between scleredema and dermatomyositis may be difficult. Scleredema usually clears within a relatively short period.

DR C W LAYMON, Minneapolis. I got an impression different from that of Dr Montgomery. I think that scleredema is fairly definite, following some acute infection. It is most unusual to have any tenderness in the skin with scleredema, and to have a complete involution within a period of ten days would be extremely unusual. It usually takes several weeks or months, even as long as eight months sometimes, for complete involution. This patient also stated that she had purplish discoloration of the lids, which might fit in with der-

matomyositis, but I could not fit it in with dermatomyositis and scleredema

**Dermatitis Herpetiformis** Presented by DR S E SWEITZER, Minneapolis

K D, white woman aged 64, was admitted to Minneapolis General Hospital on Jan 13, 1944, complaining of blisters in the axillas and groins associated with much burning pain. The lesions began in May 1939 with the same symptoms, and the patient was hospitalized at the University Hospitals in October 1939, the diagnosis of pemphigus was considered. In November and December she received seven injections of germanin. In January 1940 she received two injections of 1 Gm each of tryparsamide. This was discontinued because of narrowed visual fields. In March 1941, she was readmitted and treated with acetarsone according to the Oppenheim technic, receiving a total of 70 capsules. Continuing treatment in June 1941, she was given arsenous trioxide (Asiatic) pills ( $\frac{1}{2}$  grain [0.07 Gm] each). She remained practically free from lesions until one week before admission, at which time new bullae appeared in the axillas and groins. During her stay in the hospital, a new crop of grouped vesicles and bullae appeared, ruptured and healed. In many sites the large bullae ruptured and healed, only to have a new crop of similar vesicles appear at the periphery a week later. Potassium iodide (50 per cent) in petrolatum and 50 per cent potassium bromide in petrolatum were applied to the healed areas for a period of seventy-two hours with no reaction.

Examination shows an obese woman with clear, tense bullae in both axillas and groins. Some ruptured bullae and others filled with cloudy fluid are seen. There are pigmented areas at the site of ruptured and healed lesions.

DISCUSSION

DR S E SWEITZER, Minneapolis. The diagnosis was made with a little uncertainty, because the patient had been shown previously with the diagnosis of pemphigus, but I showed her again today for the purpose of a definite diagnosis.

DR HAMILTON MONTGOMERY, Rochester. In answer to the question whether the histopathologic picture of dermatitis herpetiformis is diagnostic, I should say no. In dermatitis herpetiformis one usually sees a great many eosinophils in the infiltrate, and the bullae show more of an inflammatory reaction and contain more cells, especially eosinophils, than one usually sees in pemphigus. Pemphigus vegetans, however, is characterized by a great many eosinophils within microabscesses. The case presented, I believe, fits in better with the cases of dermatitis herpetiformis than of pemphigus. The patient should, I believe, have a good chance of responding to treatment with sulfapyridine.

DR L H WINER, Minneapolis. At the last meeting there was a discussion on the chronic benign form of pemphigus vulgaris and dermatitis herpetiformis, and Dr O'Leary thought that they were two different definite entities. In this case clear bullae developed without any erythema or any inflammation. The lesions looked like pemphigus, and microscopically on examination of certain bullae there was no evidence of eosinophilia or of previous eosinophilia and there were no signs of inflammation. The picture looked like that of acute pemphigus with few if any inflammatory changes. However, the clinical course, the general well-being of the patient and the absence of the particular putrid odor make me think that one is dealing with chronic pemphigus or dermatitis herpetiformis. Dr Sweitzer believed that this patient

has typical dermatitis herpetiformis, as described by Duhring.

**Reticuloendotheliosis** Presented by DR S E SWEITZER, Minneapolis

(This case is reported through the courtesy of Dr George Fahr, Chief of the Medical Service, Minneapolis General Hospital, Minneapolis.)

A S, a white woman aged 52, first noted fever and weakness in May 1943, and a diagnosis was made from biopsy of sternal marrow. Nodules have appeared in the skin of the abdomen, face and scalp during the past three months and have increased in number and size.

Serologic tests for syphilis elicited negative reactions. The hemoglobin content was 42 per cent, red blood cells 1,500,000 and white blood cells 800. An occasional lymphoid cell showed reticuloendothelial characteristics. One (late telophase) mitotic figure seen.

Examination shows a poorly nourished, pale woman with multiple nodules varying from 2 mm to 3 cm in diameter. The color is a peculiar purplish brown. Some nodules are slightly raised from the surface of the skin and others, notably on the face and scalp, are decidedly elevated.

DISCUSSION

DR E M SCHLEICHER, Minneapolis (by invitation)

The question arises whether or not the lesions in this particular case were already multiple or were primary in the bone marrow at the time the patient was admitted to the hospital. Whatever the fact may be, it is noteworthy that the cutaneous lesions and the lymphadenopathy appeared several months after the disease had been diagnosed by means of a sternal marrow biopsy. I have observed 3 cases in which the lesion involved apparently the marrow organ, the lymphatic system and the skin, in the order named, several weeks to six months after the diagnosis of reticuloendothelioma of the marrow organ had been made. The lesion in this case appears to follow the same pattern. It grows in the marrow organ along the same pattern as the primary malignant lymphoma, eventually involving the entire reticulum. Both lesions have the tendency to form tumors ranging from 0.5 to 3 millimeters in diameter. It may become difficult during the terminal stage of the lesion to distinguish this lesion from a leukemic lesion, since undifferentiated, reticular cells may enter the peripheral circulation in large numbers. The short periods of high fever are interesting. The fever has been observed to be the precursor of new lesions. I prefer the term reticuloendothelioma for this lesion because of the tendency toward tumor formation and the striking sensitivity to roentgen ray therapy. I do not wish to give the impression that the best way to look for the lesion is in the bone marrow organ because the biopsy tissue revealed the lesion before the skin was involved, but I wish to point out the value of this simple procedure as an adjunct to clinical diagnosis. I have no data covering the possibility of multiple primary lesions. As to the nature of the disease, I feel the lesion is a true neoplasm. The lesion shows histologically similarities to the lesion described as "reticuloendotheliomatosis" by Symmers and Hutchison in 1939.

DR HAMILTON MONTGOMERY, Rochester. This was one of the most interesting cases presented. From looking at the histologic sections alone, one is impressed by the number of mitotic figures and of reticulum cells. I believe many pathologists would diagnose these sections as reticulum cell lymphosarcoma or, in the old terminology, "large round cell lymphosarcoma." Because of the presence of monocytes with grooving of

the nuclei, I also thought of the Schilling type of monocytic leukemia. When one takes the data as presented as a whole, the case definitely belongs with the cases of reticuloendotheliosis.

#### A Case for Diagnosis (Lupus Erythematosus?)

Presented by DR CARL W LAYMON, Minneapolis

H J, a woman aged 32, noted a roughness on her face three years ago. Since that time it has not changed a great deal, despite use of ointments, vitamin A by mouth and fractional doses of roentgen radiation.

The eruption is limited to the face and neck above the collar line. The lesions are ill defined erythematous patches without noticeable follicular dilatation or plugging. The skin does not feel infiltrated but is dry and rough like a nutmeg grater. There is no visible atrophy, although the follicular openings are hyperkeratotic. There is no scarring. Telangiectases are present on the cheeks. There is a suggestion of mottled brownish pigmentation in the erythematous patches. Histologic observations are consistent with the diagnosis of lupus erythematosus.

#### DISCUSSION

DR J F MADDEN, St Paul. I have seen a number of such eruptions, and I am not sure whether they are lupus erythematosus or rosacea. I should like to know whether any one has been able to treat them satisfactorily. In my experience such eruptions are very resistant to treatment.

DR STEPHAN EPSTEIN, Marshfield, Wis. The eruption of Dr Laymon's patient started as a well defined lesion that spread and increased in size. When one felt it, there was a roughness like follicular hyperkeratosis. I favor the diagnosis of lupus erythematosus. I have seen similar eruptions and treated them as lupus erythematosus—some responded to gold therapy—but I should not go so far as to make a definite diagnosis.

#### A Case for Diagnosis (Granuloma Annulare?)

Presented by DR H E MICHELSON, Minneapolis

N B, aged 47, noticed a papular eruption on the dorsa of both hands, which gradually extended peripherally until the entire back of the hands was involved.

Results of examination and of laboratory studies are normal.

#### DISCUSSION

DR H E MICHELSON, Minneapolis. Clinically, when I first saw the patient, I thought that the eruption was lichen planus, as it receded it resembled a granuloma annulare, and I think it is that now. He has been to Rochester, and the sections shown were taken by a physician in Chicago. No diagnosis was made there.

DR HAMILTON MONTGOMERY, Rochester. I agree with the diagnosis of granuloma annulare. In some cases there are giant cells, but the mere presence of giant cells does not establish the diagnosis of tuberculosis. I do not believe that granuloma annulare is a tuberculous disease.

#### Basal Cell Epithelioma with Chronic Lymphatic Leukemia. Presented by DR S E SWEITZER, Minneapolis

J F, a man aged 75, was first found to have chronic lymphatic leukemia in April 1940. In November 1942, there were two small nodules on each cheek below the nose. Biopsy of all lesions was performed, and two on the right cheek and one on the left were found to be basal cell epitheliomas. In December 1943, the patient re-

turned with an ulcer of the right cheek lateral to the corner of the lip of three months' duration. The margins of the ulcer had an indurated, rolled edge. No treatment was given.

Examination of the blood showed 8,500 leukocytes with 5 per cent neutrophils and 95 per cent lymphocytes. The majority of the lymphocytes were of the immature type, showing a narrow rim of cytoplasm. Occasional medium-sized lymphocytes were seen, but no cells of the mature type. Histologic sections showed chronic lymphatic leukemia cutis with invasion of a basal cell epithelioma into the leukemic infiltrate.

#### DISCUSSION

DR L H WINER, Minneapolis. The history stated that the man has been treated for three or four basal cell epitheliomas previously, and he came into the clinic with what looked like herpes simplex at the angle of the mouth where the present ulcer is. My colleagues and I watched it for a period of two weeks and could not observe any change. We then performed a biopsy and found basal cell epithelioma in a chronic lymphatic leukemia infiltrate.

#### Lupoid Sycosis. Presented by DR H E MICHELSON, Minneapolis

F S, a man aged 27, had an eruption on the face, nape and groin, consisting of follicular lichenoid papules. Gradually the areas enlarged, leaving epilated areas and superficial scars. At present the centers of the lesions are free from eruption, with activity only at the border. The serologic reaction for syphilis was negative.

#### DISCUSSION

DR H E MICHELSON, Minneapolis. I do not think that I have given all the history. This man had folliculitis of a questionable type. He was in California at the time. The follicular lesions were all grouped, and he was treated by a physician out there. He finally came back here, and I saw him. At the first, the lesions were acutely inflammatory, gradually each pustule became a nodule, and as the nodule emptied it left scars behind.

DR STEPHAN EPSTEIN, Marshfield, Wis. The patient presents that clinical picture which in Europe was called by most dermatologists lupoid sycosis and which corresponds to Unna's ulerythema. The patient presents papular lupoid nodules of the face with folliculitis-like lesions on the back of the scalp. Personally, I believe lupoid sycosis is a form of, or closely related to, sycosis vulgaris. That does not mean that I consider it a staphylococcal infection, and, incidentally, it has never been proved that it is. There are many points which speak against this generally accepted theory.

DR F W LYNCH, St Paul. In this patient the end result closely resembles the condition which Savatard has recently described as "honeycomb atrophy" (*Brit J Dermat* 55 259 [Nov] 1943).

#### Porokeratosis (Mibelli). Presented by DR S E SWEITZER, Minneapolis

J K, a white boy aged 15, first noted a lesion on the right side of the neck and a smaller lesion on the left side of the neck and one on the right index finger four years ago. These have grown slowly since that time but have caused no symptoms.

On examination, a hard, circinate, elevated lesion with a sharply demarcated raised margin is noted on the right side of the neck and a similar but smaller

lesion on the left side of the neck. There are small flat verrucous lesions on the forefinger.

## DISCUSSION

DR H E MICHELSON, Minneapolis. These lesions belong to the nevroid condition. There is nothing especially to say. One can destroy most of the lesions and get fairly good results. It is amazing how common reports of this disease are in the Italian literature.

## A Case for Diagnosis (Atrophic Lichen Planus?)

Presented by DR S E SWETZER, Minneapolis

J O, a man aged 59, was admitted to the Minneapolis General Hospital on Jan 22, 1944, complaining of weakness, loss of weight and a burning sensation in the soles of one month's duration. In July 1942 he first noticed several fiery red spots on the lateral surface of the right leg, midway between the knee and the ankle. The initial lesions were not elevated or sore and did not itch. They grew progressively larger and coalesced to form large irregular plaques. A few appeared on the trunk. During the past four months, these plaques have become noticeably thickened and fissures have appeared. He received no medication, with the exception of a small amount of solution of potassium arsenite and syrup of hydriodic acid. The color of the lesions changed from fiery red through a lilac color to a dusky purplish brown.

Biopsy of bone marrow interpreted by Dr E M Schleicher was reported as showing no evidence of pernicious anemia, although there were a macrocytic tendency, hyperplasia of myeloid tissue and a tendency to produce monocytoïd histiocytes. Some of these cells contain lipochromes, and an occasional one contains light to dark brown granules which could not be demonstrated to be melanin. The marrow pattern does not suggest the presence of a malignant melanoma in the marrow organ, although it appeared that hepatic impairment was present. Melanin was found in the urine on January 24 and 31 and February 1, and was not found on January 29 and February 2.

Serologic reactions for syphilis were negative. A blood count showed hemoglobin content, 80 per cent, erythrocytes, 3,440,000, and leukocytes, 3,800, with 59 per cent neutrophils, 3 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils.

Examination shows purplish brown lichenified plaques on the legs, thighs, trunk and arms. In lichenified areas a few angular papules can be seen.

NOTE.—Since the laboratory work was reported, we have shown that the substance reported as melanin in the urine was not melanin but a derivative of some phenol or possibly acetylsalicylic acid, hence ferric chloride turned the urine black, but on the days on which the patient did not receive any acetylsalicylic acid the reaction was negative. On the days following the administration of the drug, they were positive.

## DISCUSSION

DR HAMILTON MONTGOMERY, Rochester. The lesions on the elbows and knees were suggestive of acrodermatitis chronica atrophicans. Other areas show changes suggestive of poikiloderma vasculare atrophicans of Jacobi. The histologic sections were consistent with the latter diagnosis, including atrophy of the epidermis with increased pigmentation, mild lichenification and liquefaction degeneration of the basal cell layer. I am, however, among those who have increasing doubts as to poikiloderma being a definite entity. Many lesions

described as poikiloderma have proved to be due to lymphoblastoma, others secondary to syphilis, lupus erythematosus, dermatomyositis and even atrophic lichen planus. If this represents a drug eruption, it is a most unique one. I am inclined to agree with the diagnosis of lichen planus.

## LOS ANGELES DERMATOLOGICAL SOCIETY

WILLIAM H GOECKERMAN, M D, *Chairman*

CLEMENT E COUNTER, M D *Secretary*

Feb 8, 1944

## A Case for Diagnosis (Dermatitis Herpetiformis, Infectious Eczematoid Dermatitis?) Presented by DR ANKER K JENSEN

M H, a man aged 32, a carpenter, began to have an eruption on the flexor surfaces of the legs about one year ago. This gradually cleared up. Three weeks ago the present eruption appeared in groups on the legs. There was also a dermatitis in the right axillary area, with some swelling of the lymph nodes. There is severe itching.

Treatment in the past three weeks has included the following local therapy: weekly fractional doses of roentgen rays, antipruritic lotion, 5 per cent sulfathiazole ointment, and 2 per cent aqueous solution of gentian violet medicinal.

## DISCUSSION

DR SAMUEL AYRES JR. This case is somewhat atypical. I thought that the disease was infectious eczematoid dermatitis until I saw what appeared to be a fresh lesion on the leg, which was rather typical of dermatitis herpetiformis, a kidney-shaped bleb. The eruption, however, is not as symmetric as one would expect dermatitis herpetiformis to be. I should have to observe such a case a little longer before making a final diagnosis.

DR L F X WILHELM. A number of lesions on the arms resembled dermatitis herpetiformis. A definite tendency to grouping of the lesions was noted.

DR W H GOECKERMAN. I believe that this is an infectious eczematoid dermatitis. I have seen an unusually large number of eruptions of this type in the last year, probably as many as I have seen in all the years of my practice before. I have searched for a common factor, but I have been unable to find any, as all these patients vary greatly in occupation and in general economic condition. The best guess as to the common background is a nervous exhaustion factor. All the patients complain vigorously of their lesions, even when only a few are present, much as this patient does.

DR A FLETCHER HALL. I have felt myself at a loss to make diagnoses in many such cases and am inclined to call the disease infectious eczematoid dermatitis for want of a better classification. The only common ground I can suggest is the possibility of a dissemination of some lesion following injudicious treatment. I have seen such eruptions, often severe, which apparently followed the use of sulfathiazole ointment. I should hesitate to call them a sulfonamide dermatitis, but it appears that a great many of the eruptions I find difficulty in classifying have followed the use of some such medication.

DR KENNETH STOUT. From the history I discovered that the eruption began one year ago behind one knee.



There were moderate varicosities on that leg. I felt that the eruption there might have been associated with a stasis factor having a superimposed infectious eczematoid dermatitis. I also thought of the possibility of sensitivity to sulfathiazole ointment, having observed similar lesions on other patients after sulfathiazole ointment had been used.

DR KENDAL FROST. I am not willing to make a definite diagnosis. I have seen infectious eczematoid dermatitis superimposed on dermatitis herpetiformis, or a dermatitis herpetiformis which suggests infectious eczematoid dermatitis. It is difficult at times to catch dermatitis herpetiformis in an eruptive phase which is characteristic. I believe this case can be better diagnosed by subsequent observations over an extended period.

DR ANKER JENSEN. When I first saw this patient, I felt that he was suffering from an infectious eczematoid type of dermatitis. However, the eruption has been spreading rather than improving, and it has taken on many of the characteristics of dermatitis herpetiformis. It is important that an accurate diagnosis be arrived at promptly, because he is under contract to the Government for construction work overseas.

#### A Case for Diagnosis (Ichthyosis Hystrix?) Presented by DR ANKER K JENSEN

P. N., a girl of 7 years, at the age of 6 weeks had an eruption on the joint areas. Gradually this has spread to the feet, hands and body, although at the age of 3 years her skin was almost completely normal.

The soles and palms have decided hyperkeratosis. The trunk and thighs show thickening of the skin with discoloration from light brown to almost black pigmentation. There is much tendency for the lesions to be arranged in streaks generally following lines of cleavage. The heavier, thicker lesions tend to lose the keratinous material that characterizes them. This material crumbles away, leaving a slightly rough but almost normal surface.

Therapy has included the administration of thyroid and large doses of vitamins A and D.

#### DISCUSSION

DR M. E. OBERMAYER. The term ichthyosis hystrix is not a happy one, as the disease has no relation to ichthyosis. The keratotic type of nevus unius lateris is a better designation, as it seems to be the generally accepted term for the prenatal disturbance characterized by intermittent bands of keratotic plaques of a brownish or blackish color which on histopathologic examination show banal chronic inflammation and a varying amount of hyperkeratosis and parakeratosis. The unusual feature in this case is the wide and bilateral distribution.

#### A Case for Diagnosis (Glomus Tumor?) Presented by DR MAXIMILIAN E. OBERMAYER

H. G., a woman aged 22 years, was presented before the Los Angeles Dermatological Society, on Feb. 9, 1943 (ARCH DERMAT & SYPH 48:322 [Sept.] 1943). Since that time the swelling has become more pronounced and tenderness has increased to such an extent that at times the patient is unable to endure the pain caused by contact with blankets or sheets. The patient is presented again, prior to surgical excision of the lesion.

#### DISCUSSION

DR H. C. L. LINDSAY. The tenderness is not over the brown part but below it. Above the brown part

there is a streak of vitiligo. The area over the brown part is much softer than the other tissues. There is slight induration below and to the front. Apparently pain is minimal tonight. The lesion is shaped like a fan, with its obtuse angle at the upper and posterior part and the distal part, toward the foot, semicircular. It looks to me as if the patient had had an injury in that area and pigmentation had followed.

DR A. FLETCHER HALL. If it is a glomus tumor, it is the largest I have seen. The history of swelling and tenderness on some days is suggestive, and I still favor that diagnosis. I believe that such tumors are noted more frequently on the digits because in that location their tenderness is more noticeable, particularly under the nail. I have seen glomus tumors on the midportion of the arm, and I suppose that they can occur on the midportion of the leg.

DR W. H. GOECKERMAN. I will agree with the diagnosis of glomus tumor. The location, in my experience, is a most unusual one.

DR M. E. OBERMAYER. Dr. Lindsay was misled by the pigmentary and atrophic changes which were present in the form of a circumscribed macule on the skin above the lesion. This change was produced by local application of acid performed some years ago by a physician for purposes unknown to me. It has nothing to do with the problem in question. It seems that Dr. Hall's original suggestion of a glomus tumor may be correct. If so, the size and location of the lesion are unusual. I wanted the members to see the patient before surgical removal of the tumor.

#### Kaposi's Sarcoma Presented by DR KENNETH McLARAND (by invitation)

About ten years ago D. C., a Jewish man aged 71, who was born in Poland, began to have pruritus and scaling of the feet, especially the left foot. Treatment afforded little relief, and in recent years he has resorted to soaks in strong solution of sodium hypochlorite and saponated solution of cresol and to vigorous rubbing with a stiff brush. The eruption has gradually developed to its present state, and there has recently been more generalized pruritus, especially of the right foot.

There is moderate swelling of the left foot and leg. There is a tumor on the lower anterior aspect of the leg, 5 cm in diameter, with raised firm borders and ulcerated center. On the remaining surface there are numerous nodules pressing close on each other. Some are deep and rather firm, particularly those near the toes on the sole. Others are soft and appear vascular. Edema is present. There is a large trophic ulcer on the heel. Much pruritus is present. Biopsy sections were taken from the large tumor and from three smaller nodules, including one on the sole.

A total of 4,320 r of roentgen rays was applied between Jan. 25 and Feb. 4, 1944. This was given to the large lesion in four treatments, and there has been approximately a 50 per cent decrease in size.

#### DISCUSSION

DR L. F. X. WILHELM. I believe that the lesion is a Kaposi's sarcoma. The patient said it started as a reddish violaceous lesion.

DR NELSON PAUL ANDERSON. I have seen this patient before, and I suggested to Dr. McLarand that he present him. I believe that this man has typical manifestations of Kaposi's sarcoma. The nationality of the patient, his age, the location of the eruption and the lesions themselves all speak in favor of such a diagnosis.



Also, on his right foot there are four or five purplish pigmented macules which are suggestive of the early stages of this disease. The unusual feature of the eruption is that the lesions are large and look like bullae from which one might express much fluid. I think that the process has metastasized and involved the regional inguinal lymph nodes, producing a secondary lymphedema. This has involved practically the entire left leg. In addition, there is undoubtedly some secondary infection, perhaps a low grade cellulitis, resulting from the open ulceration on the ankle. Thus, at least two factors enter into the production of the lymph stasis. I feel that the process is of longer duration than the patient admits.

DR H C L LINDSAY I have seen a lesion similar to this due to tuberculosis involving the thigh bone with resulting lymph stasis which produced a lesion similar to elephantiasis of the leg. I think tuberculosis ought to be considered in making an ultimate diagnosis.

DR W H GOECKERMAN I have never seen a Kaposi hemorrhagic sarcoma with secondary lesions of this type, but I think the lesions on the other foot are strongly suggestive of that diagnosis.

DR NELSON PAUL ANDERSON Dr McLarand has made several biopsies. I think there is no question but that they are typical of the hemorrhagic sarcoma of Kaposi.

DR M E OBERMAYER I have never seen Kaposi's sarcoma associated with such pronounced bullous lymphedema. If the diagnosis were not confirmed by biopsy, I should have suggested the possibility of trophic neural changes which may manifest themselves by bullous lymphedema and elephantiasis hyperplasia.

DR KENNETH McLARAND I have wondered whether or not the years of self treatment have had something to do with the disease. The patient has bathed the foot almost daily in strong solutions. I understand the itching has been present for more than ten years and always had been attributed to a fungous infection. When I first saw the large lesion, it was much more pronounced and was suggestive of a squamous cell epithelioma. I was unable to account for the nodules on the leg and foot, some of which resembled the pea-shaped basal cell type epithelioma not infrequently seen on the face. Plantar lesions were flattened and wartlike, owing, I assumed, to scratching and pressure. Many of them could be felt better than they could be seen. Sections from several of these lesions, including one from the sole, were all reported as being histologically the same.

#### A Case for Diagnosis (Multiple Ulcerations of the Legs of Undetermined Origin?) Presented by DR SAMUEL AYRES JR

E G, a man aged 57, has been presented before the Society previously, on Oct 12, 1943, because of numerous ulcerations of the legs which began in May 1942, following trauma by knocking his leg against a desk.

Many types of treatment have been given. At one time the leg was nearly healed while the patient was hospitalized and using chlorohydroxyquinoline ointment, among other things. The patient later became sensitive to this drug and its use had to be discontinued. The ulcerations have resisted many types of local treatment including antiseptic wet dressings, roentgen irradiation, sulfadiazine, sulfathiazole and tyrothricin, both as wet dressings and ointment. The patient also received autogenous vaccine intravenously and nine intravenous injections of mapharsen, 60 mg each, as well as fifteen

intramuscular injections of thio-bismol and later seven intramuscular injections of bismuth salicylate. Except for the initial improvement under chlorohydroxyquinoline ointment the ulcerations have persisted, some beginning to heal and others appearing. Finally, the patient was given intramuscular injections of stibophen (sodium antimony bicatechol disulfonate of sodium) which was given empirically and with the thought that the condition might be leishmaniasis. Search for leishmaniasis, both in biopsy specimens and in scrapings from the ulcerations, was negative. The patient has received fourteen intramuscular injections of stibophen, 5 cc each, approximately twice a week. The ulcerations now are at least 95 per cent healed.

The ulcerations have been somewhat verrucous in nature, resembling the appearance seen in blastomycosis or in bromide granulomas, but both of these possibilities have been carefully considered and ruled out.

The final diagnosis is still obscure, but the patient is presented to show the apparent therapeutic effect of an antimony preparation.

#### DISCUSSION

DR SAMUEL AYRES JR The eruption has continued with lesions partly healing and new ones developing, especially on the border of the old lesions. A diagnosis has never been established in this case. At first the lesions resembled blastomycosis or a bromide eruption, and I even thought of atypical leishmaniasis, but no leishmania bodies were found. Empirically we gave stibophen intramuscularly, and the eruption has made a spectacular change since the first two or three injections. At the present time the ulcers are practically all healed, with one or two exceptions.

NOTE—The next report on this patient's progress (one month later) stated that ulcers had reappeared even while stibophen was being used.

#### A Case for Diagnosis (Dystrophy of Nails, Cause Undetermined?) Presented by DR SAMUEL AYRES JR

H M, a woman aged 61, was presented previously before the Society, in June 1942, and at that time no definite diagnosis was offered. The disease of the nails began in November 1940 and has been persistent ever since. All the finger and toe nails are involved, and all of the finger nails at the present time reveal longitudinal striation. One shows longitudinal ridging. The dorsal ends of the nails are opaque and slightly thickened, while the left thumb nail shows a brownish discoloration. There is also some splitting and fraying of some of the nails and separation of the nail from the nail bed along the distal portions. The toe nails, especially of the medial three digits of both feet, show longitudinal striation, opacities, splitting and fraying as well as separation of the distal portion from the nail bed.

Repeated scrapings, from both finger and toe nails, examined by direct microscopic observation and by culture, have been consistently free of pathogens except at the time of the patient's first visit, when *Monilia* was found in specimens from the finger nails by culture on two occasions and *Trichophyton purpureum* was isolated on one occasion from the toe nails. Since then on eight occasions no organisms of any kind have been found either by culture or by scraping.

A variety of treatment has been given, including fractional doses of roentgen rays, ointment of benzoic and salicylic acid N F, both full and double strength, combined with grinding of the nails with a dental drill,

thyroid by mouth, vitamin A by mouth in doses of 75,000 U S P units daily and vitamin B complex, over a considerable period. Kahn and Kline tests of the blood elicited negative reactions. A routine blood count was normal, and the patient has been under medical observation without any serious defects having been discovered. She is presented for further suggestions as to diagnosis and treatment.

## DISCUSSION

DR CHRIS HALLORAN Dystrophies of the nails present a problem as to cause and therapy. In the last few years I have seen a number of women with dystrophies for which I suspected lacquer nail polish to be either the cause or a contributing factor. This woman gives no history of having applied lacquer to the nails.

DR PAUL FOSTER This woman had typical vitiligo, and it has been my experience that frequently there is an associated psoriasis in some instances and arthritis in other instances. In view of the detachment of the nails in a typical psoriatic manner, I suggest the diagnosis of psoriasis.

DR A FLETCHER HALL I seem to have had a good many such cases during the past two years. At first I observed that the majority of the patients were women, but more recently I have treated numerous men for dystrophies which were similar to the others and identical with this one. I do not believe that there is any connection with the use of nail lacquer, and I do not see how physically it could have any effect. As far as treatment is concerned, I have been fortunate in getting satisfactory results in a large proportion of cases by use of thyroid extract by mouth and liver extract and thiamine hydrochloride intramuscularly. If the patients will come in twice a week for three or four months, I think that a growth of nail can be produced which will stick to the nail bed all the way out.

DR ANKER JENSEN The patient states tonight that her finger nails have started to grow. I feel that many diseases of the nails are of metabolic origin, and this patient was suffering from low blood pressure, anemia and a low basal metabolic rate. These conditions have been corrected, and she feels that her general health is much improved. My feeling is that the correction of these conditions is responsible for the improvement of her nails.

DR M E OBERMAYER I should also consider functional factors in this patient. She shows features of emotional instability, and her complaints are of a functional rather than an organic nature. The simultaneous presence of vitiligo is to me another indication of an emotional tension background, which should be investigated.

DR KENDAL FROST I agree with Dr Foster that the appearance is more that of psoriasis than of any other entity.

DR SAMUEL AYRES JR I have not seen the patient very often during the past few months. She had been under the care of a competent internist for nearly a year, building up her blood and taking vitamins, and personally I cannot see that the nails look much different. I had previously considered psoriasis, and I gave her a course of fractional roentgen ray therapy. She now immerses her hands in hot paraffin and lets it cool and remain on for several hours a day, which she thinks has helped. Personally I do not think that the nails look much different. All the general factors have been considered and treated and the disease still persists.

A Case for Diagnosis (Psoriasis?) Presented by  
DR KENNETH McLARAND (by invitation)

A H W, a man aged 35, suddenly began to have numerous "livid" spots on the sides of the trunk and on the upper extremities. This onset was six months ago. Each lesion enlarged rapidly and presented central scaling. There has been moderate pruritus. This eruption cleared in three weeks. The present lesions are in the form of a generalized eruption consisting of numerous scattered slightly erythematous and slightly raised papules. They vary from 1 to 15 mm in diameter. The larger lesions have more prominent borders and fawn-colored centers, covered with fine scales. In places a confluence of smaller lesions has resulted in ringed configurations. The eruption is most evident on the sides of the chest, particularly under the arms. It is also present on the extensor surfaces of the arms and thighs. It was not possible to demonstrate fungi in the scales.

Engman's lotion (mercury bichloride, resorcin, glycerin and 70 per cent alcohol) applied twice daily, together with ultraviolet irradiation twice weekly resulted in almost complete disappearance of the eruption within three weeks.

Within a month there was a gradual recurrence. Resumption of the same treatment a week ago has been followed by about the same rate of improvement as before.

## DISCUSSION

DR H C L LINDSAY If the patient had not told me that there was a great deal of itching, I should have thought more of parapsoriasis than of psoriasis or possibly of lichen planus.

DR A FLETCHER HALL I thought that this was possibly a case of pityriasis lichenoides chronica.

DR L F X WILHELM I think that the eruption is probably parapsoriasis.

DR SAMUEL AYRES JR I thought that it was pityriasis lichenoides chronica.

DR KENNETH McLARAND When I first saw the patient, the lesions were scarcely raised at all. There was fine scaling, typical of that seen in pityriasis rosea. At any rate, I treated him for that disease, and in three weeks the skin was entirely clear, but the eruption recurred a month later, at which time the lesions were more pronounced than before and more characteristic of psoriasis, although the configuration was most unusual and the distribution more suggestive of pityriasis.

DR W H GOECKERMAN I should be inclined to a definite diagnosis of psoriasis. It is true that the lesions are not of the usual type, but the scales are readily removed by scraping and present fine bleeding points. Against parapsoriasis is the fact that the individual lesions disappear, only to have new ones appear.

DR KENNETH McLARAND After the first three weeks' treatment all lesions were gone, and the eruption has again improved about 50 per cent after one week's treatment.

Lupus Vulgaris with Prickle Cell Epithelioma of the Nose Presented by DR SAMUEL AYRES JR

E V, a woman aged 61, whose mother died of tuberculosis, states that the onset of her present illness occurred at 17 years, with a lesion on the upper lip. She came to the United States at the age of 21 years. At the age of 35 years the lesion, which had been arrested by some kind of cauterization, began to spread and has progressed slowly until now. About six months

ago an ulcerative lesion appeared on the nose, and it has been getting larger. The patient has a somewhat slender appearance. There is an extensive eruption on her face, making a butterfly-shaped lesion across the bridge of her nose, extending out onto the cheeks, down onto the sides of the chin and onto the forehead between the eyebrows. It is well margined and slightly elevated. There are extensive scarring and destruction of the lower part of the nostrils. Especially about the borders but also within the plaques are discrete and grouped typical soft "apple jelly" nodules.

On the dorsal aspect of the nose, especially to the left, is an extensive, approximately quarter-sized elevated nodular plaque with rounded borders and a rough warty-looking surface which covers most of the dorsum of the nose and is crusted and ulcerated centrally.

The patient has been referred to a plastic surgeon, who proposes to remove the epithelioma by surgical cauterization and to replace the lupus tissue by skin grafts.

#### DISCUSSION

DR SAMUEL AYRES. The case is typical. I presented the patient because lupus vulgaris is not common here. The patient was born in Holland, and the lesion has persisted in spite of her coming here at an early age. The treatment of the epithelioma will be surgical and will require much plastic reconstruction, but obviously this cannot be done on account of the lupus vulgaris. A competent plastic surgeon said that the lesion on the nose could be destroyed surgically and thereafter the lupus tissue could be removed surgically also and replaced by skin graft. In the January 1944 issue of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY an article described replacement graft for treatment of a small lesion of lupus vulgaris on the upper lip. Has any one had experience in treating lupus vulgaris by grafts? It is considerable of a technical problem in this case.

DR M. E. OBERMAYER. I agree with Dr Ayres that surgical excision would be feasible only if the lesion were of limited size. For this patient, surgical measures are distinctly contraindicated.

DR W. H. GOECKERMAN. Soon after World War I, at least within a few years after that time, I saw a number of patients with practically identical lesions treated with plastic surgical operations, but in my opinion the work was not successful. It is, of course, entirely possible that improvements in the technic will now produce better results.

#### Rothmund's Syndrome Presented by DR NELSON PAUL ANDERSON

A B, a man aged 56, was presented before the Society on Nov 9, 1943, with a diagnosis of Rothmund's (Werner's) syndrome. Premature baldness accompanied with premature graying of the hair, vitiligo, scleropoikilodermatous cutaneous changes and characteristic habitus were mentioned as characterizing this syndrome. Since that time a sugar tolerance test has been made. This revealed definite disturbance of the carbohydrate metabolism. The fasting blood sugar level was 107 mg per hundred cubic centimeters. One half hour after the sugar meal the blood sugar level was 155 mg. One hour later it was 164 mg, an hour and one half later it was 172 mg, and at the end of two hours the level was still 154 mg. All specimens of urine after the sugar meal were given gave positive qualitative reactions for sugar. On Nov 16, 1943, he was given vitamin A in a dosage of 75,000 U. S. P. units daily. A report from his ophthalmologist states that the entire retina and

choroid areas show a generalized pigment disturbance. There is decided improvement of all symptoms.

#### DISCUSSION

DR NELSON PAUL ANDERSON. A group of reports in the literature describe a syndrome with the following characteristics. A loss of hair early in life and premature canities occur, as the process progresses alopecia totalis develops, disturbances of vision occur, sometimes disturbances of hearing begin, disturbances of pigmentation are seen, particularly vitiligo occurs, and vitiliginous changes in the choroid and retina also may appear. There is evidence of metabolic change by a lowered sugar tolerance. Calcium may be increased in the blood. Associated with this syndrome are changes in the skin which have never been particularly studied by dermatologists but which have been described by internists and which Dr Oppenheimer has termed a scleropoikiloderma. This man had scaling red lesions on the arms and trunk and a peculiar, atrophic-like wrinkling of the skin. In just what group of disorders this syndrome should be placed I do not know, but I think that some day some one will be able to classify such cases in a distinct group. I have presented this patient again tonight to show what remarkable improvement the administration of vitamin A would accomplish.

#### Black Hairy Tongue Presented by DR SAMUEL AYRES JR

G I, a white woman aged 36, had an ocular muscle imbalance. She has been taking belladonna for several years for "bowel spasms." Until two months ago she had used proprietary lozenges for a streptococcal infection of the throat. Ten per cent hydrogen peroxide has been used as a mouth wash three times a day for several years following an attack of pyorrhea. She has also been taking 2½ grams (0.16 Gm) of thyroid daily for the last four years.

The black coating on the tongue began to develop about a month ago. She describes a sensation of having sand on her tongue. The disease has been progressive.

The lesion is limited to the dorsal surface of the tongue, which, except the distal quarter, is covered with a thick, furry coating of a dark brown color. These long hairy particles can easily be picked off.

Direct microscopic examination did not reveal fungi. Culture on several types of medium revealed a variety of bacteria but no fungi.

#### DISCUSSION

DR A. FLETCHER HALL. About six months ago I saw a man with a white hairy tongue. I had seen the black type before but never white. It showed a general involvement of the entire dorsal aspect but with longer hairs in the region of the circumvallate papillae. On microscopic examination they appeared to be elongated strings of epithelial cells, presumably elongations of the papillae. I, too, examined and cultured for fungi but found none.

DR ANKER JENSEN. As to therapy, I suggest applying trichloroacetic acid to the area, and I believe the results would be good.

DR CLEMENT E. COUNTER. I have had a case in which brown hairy tongue responded to treatment with trichloroacetic acid. Improvement was gradual. About three months was required to cure the lesion.

DR SAMUEL AYRES JR. This case interested me from an etiologic standpoint. Authorities are vague. This woman has been taking belladonna for several

years because of intestinal spasms. It occurred to me that perhaps the use of belladonna had diminished her salivary secretion to an extent which would permit a coating on the tongue to develop. If the mouth were dry, there might develop a certain amount of coating. Another possibility is the use of throat lozenges. This patient says that she has not used any for the last couple of months. She wears a patch over one eye on account of muscle imbalance. She has washed her mouth with 10 per cent hydrogen peroxide three times a day for three years because she once had pyorrhea

#### A Case for Diagnosis (Melanoderma?) Presented by DR MAXIMILIAN E OBERMAYER

R Y, a white boy aged 9 years, was seen first on Nov 26, 1943. At the age of 6, macules appeared on the ankles, the lesions remained confined to this region for two years, then the eruption spread slowly to the legs, thighs and buttocks, and during the last three months, since he was first examined, the axillas and arms have become involved. He says that he has not taken any drugs. He does not use pink toothpaste or eat pink cakes and candy. Since the time of the first visit (ten weeks ago) the lesions in general have become slightly lighter and some of them (e g, around the axillas) have disappeared without leaving traces. A few new lesions have formed on the legs and thighs.

The eruption consists of macules, varying from 1 to 3 cm in diameter and of various configurations, densely aggregated on the legs and thighs and more sparsely distributed over the buttocks, around the axillas and the flexor surfaces of the forearms. These surfaces are smooth and have a medium brown color, only part of the lesions exhibit a dusky erythematous hue.

Mucous membranes are not involved. Wheals could not be produced by friction.

On the upper part of the back there is a conglomeration of depigmented macules, which has been present since birth (nevus anemicus).

Biopsy sections stained with hematoxylin and eosin revealed a normal epidermis with a loose corneous layer. In the dermis there was a pronounced perivascular infiltrate which consisted mainly of lymphocytes. Silver stain revealed large amounts of pigment present in irregular distribution in the basal cell layer. Iron stain did not reveal the presence of hemosiderin.

#### DISCUSSION

DR KENDAL FROST: I saw this boy with Dr Obermayer some time ago, and I thought then that the eruption would turn out to be typical urticaria pigmentosa. The most interesting thing to me is that some of the axillary lesions present when I first saw him have disappeared.

DR W H GORCKIRMAN: I saw this patient some months ago. At that time I, too, was rather puzzled as to the diagnosis. My first impression was a fixed drug eruption, but the history and behavior do not substantiate this diagnosis. The best suggestion I could make was that the eruption was probably of toxic origin, and I suggested a general physical study with special reference to foci of infection. New lesions present a picture of low grade inflammation. As this subsides, the pigmented spots remain.

DR M E OBERMAYER: I realize that the diagnosis of melanoderma is etiologically meaningless. When this patient was first seen, a preliminary diagnosis of urticaria pigmentosa was made. This diagnosis could not be confirmed by biopsy. My next considerations were hemosiderosis and a drug eruption of the fixed

type, because the section showed a considerable amount of melanin in the basal cell layer of the epidermis. The term melanoderma appears justified. The eruption is undoubtedly of internal origin, perhaps associated with glandular disturbances, though—as I was assured by the child's physician—no abnormalities could be detected on general examination.

#### Dermatophytosis Due to *Trichophyton Purpureum* with *Monilia* Infection of the Mouth Presented by DR SAMUEL AYRES JR

P T, a white man aged 24, was first seen in March 1941. Then the eruption had been present about four months and consisted of ill defined, erythematous, scaly lesions on the soles and sides of the feet with dystrophy of several toe nails. The patient has been under almost continuous treatment since that time, without benefit. He is underweight. All aspects of the feet are involved, with diffuse, dry scales covering the soles and extending between the toes and also up on to the sides and tops of the feet and ankles. The lesions are sharply margined, erythematous and scaly. The patient also presents similar lesions on the buttocks. On previous occasions he has had a similar type of lesion involving the face and anterior aspects of the ears. A number of toe nails are thickened, crumbly and discolored. The patient also presents areas of redness, with some appearance of atrophy, and a few white flecks involving the mucous membrane of the mouth.

Many examinations have been made both by microscope (potassium hydroxide mounts) and by culture on Sabouraud's medium. Masses of fungous filaments have been found consistently on each examination from all of the areas examined, and *Trichophyton purpureum* has been grown on culture of scrapings from the face, from the buttocks and from the feet. *Monilia albicans* has been grown on two occasions from lesions in the mouth.

The urinalysis revealed nothing significant, and the blood sugar level was normal.

Local treatment has included the use of full strength and double strength ointment of benzoic and salicylic acid N F. This ointment combined with 3 per cent chrysarobin was not tolerated. An ointment containing 6 per cent each of salicylic acid and sulfur appears to help the lesions on the body but has had no effect on the lesions on the feet. Castellani's paint, tincture of iodine, 5 per cent sulfathiazole ointment and chlorohydroxyquinoline ointment are some of the other agents which have been applied without success. Two of the lesions on the dorsal aspect of the feet were frozen with solid carbon dioxide, and two were painted with iodine and subsequently frozen with solid carbon dioxide without effect other than a severe blistering reaction. Internally, the patient has received 5 mg of riboflavin three times a day for several months at a time, as well as Stuart's formula containing all of the vitamins, plus iron and manganese. Vitamin A, 50,000 U S P units three times a day, has been used over a considerable period.

The patient is presented for further therapeutic suggestions.

#### DISCUSSION

DR SAMUEL AYRES JR: I was hoping some one would have some new suggestions for treatment. The interesting thing about this patient is that the lesions on his face and body from which *Trichophyton purpureum* have been isolated have apparently responded well to ointment of benzoic and salicylic acid and to salicylic acid and sulfur ointment. Those on the feet are absolutely untouched by anything used. The patient

has had lesions in the mouth more characteristic of moniliasis than those observed today. Monilia has been demonstrated in the oral lesions but not *Trichophyton purpureum*. It is a serious problem from a therapeutic angle.

DR KENDAL FROST Has freezing with ethyl chloride been tried?

DR SAMUEL AYRES JR I have tried that on one part but not extensively yet. I used a solid carbon dioxide pencil, rubbing it over the skin. This was done once, but the organisms are still plentiful.

**A Case for Diagnosis (Perioral Chloasma of Poor, Erythrose Peribuccale Pigmentaire de Brocq?)**  
Presented by DR NELSON PAUL ANDERSON

K P, a white woman aged 27, has had a discoloration of the skin about the edge of the mucous membrane-vermilion border of the lips for the past ten years.

The present examination reveals a linear reddish brown pigmentation on the skin just above and below the vermilion border of the lips. It was slightly more evident on the lower lip.

DISCUSSION

DR NELSON PAUL ANDERSON I do not know exactly what this is or where to place it. I believe that these exemplary perioral chloasma are the same as erythrose peribuccale pigmentaire de Brocq. I have seen about 2 such cases. At times the pigmentation is decided, and at other times it is difficult to ascertain. Ormsby and Ebert made a similar remark about a patient whose face was involved to a considerable extent.

**A Case for Diagnosis (Plantar Papilloma with Ulcer?)** Presented by DR ANKER K JENSEN

E M, a man aged 43, began having some thickening of the plantar surface of the right great toe and of the sole just proximal to the great toe. Before coming to me, the patient was treated by a chiropodist with acids and pads.

The present examination reveals a pea-sized ulcer on the plantar surface of the right great toe that is moist. On the right sole adjacent to the great toe there is a deep hard margined ulcer about 1 cm in diameter.

Treatment has consisted in (1) intramuscular injections of bismuth sodium tartrate at weekly intervals for eight weeks, (2) 600 r of roentgen rays applied to the lesion on the sole, (3) electrodesiccation of the lesion on the toe followed by 1,000 r roentgen radiation.

A biopsy section has revealed verruca vulgaris. The Wassermann reaction of the blood was negative, and the urine was normal.

DISCUSSION

DR SAMUEL AYRES JR I thought of two possibilities: (1) a trophic ulcer in a diabetic person and (2) a trophic ulcer on the basis of tabes. I did not have the opportunity to check the patient's reflexes, but I think those two possibilities should be considered in this case.

DR L F X WILHELM If either of the possibilities suggested by Dr Ayres is correct, I think that the less local treatment that is given the patient the better.

DR NELSON PAUL ANDERSON The man has warts on his foot.

DR SAMUEL AYRES JR That does not preclude a trophic ulcer.

DR W H GOECKERMAN This is essentially a trophic ulcer, and the first thought is of some disease of the nervous system, including tabes. In the absence

of a critical neurologic examination, I saw nothing in the patient to substantiate this. While the history may not exactly suggest an undesirable result of actinotherapy, I should not overlook this possibility. Therapy with radium and even with screened roentgen rays could produce a picture of this type. I believe that the urine gave a negative reaction for sugar. It is entirely possible that overtreatment of a plantar wart has injured the periosteum and produced a mild osteomyelitis.

DR NELSON PAUL ANDERSON I think it would be a good idea, before anything further is done, to have a diagnostic roentgenogram of the toe, especially if there is a discharge in the area of this trophic ulcer. There might be an underlying osteomyelitis. I have not seen a case of radiodermatitis from the fluoroscopes used in shoe stores, but I feel that such equipment is a potential hazard to the public. Children in particular might be overexposed to roentgen rays, in complete ignorance of any such exposure.

DR SAMUEL AYRES JR It seems to me that the absence of pain is of considerable significance. Ordinarily, a lesion of that sort, being walked on, would cause a great deal of pain. I think a neurologic examination and spinal puncture would be in order.

DR ANKER JENSEN The discoloration on the toe and medial aspect of the foot is due to a severe inflammation that had developed before the patient came to see me. He received only  $3\frac{1}{4}$  skin units of roentgen rays postoperatively to the lesion on the toe. He had a papilloma on the sole. This was well shielded. This lesion responded well, but he had numerous other smaller ones on the heel. Because of this fact, he received injections of bismuth at weekly intervals. I went into his history thoroughly to see if there was a possibility of his having syphilis. No evidence was discovered to substantiate that diagnosis.

**Localized Scleroderma** Presented by DR CLEMENT E COUNTER

R S, a boy aged 7 years, began to notice the present facial lesion about six months ago. It was thought to be ringworm. About that time he was seen by a surgeon, who prescribed a phenylmercuric nitrate preparation locally. This local application seemed to improve, the brown discoloration.

The present examination reveals a brown, irregular, oval patch on the left side of the face. This extends from the left side of the chin to the left side of the neck just below the left ear. This patch measures 3 to 5 cm in width and 15 cm in length. Toward the chin there is an ivory-colored, round portion of the lesion which is about 2 cm in diameter. This part of the lesion is indurated and brawny.

DISCUSSION

DR L F X WILHELM I agree with the diagnosis as presented.

DR CLEMENT COUNTER I thought it was interesting to see this rather rare disease in a child. The point in question is what to do for him. Should one use roentgen rays on such a child? I have seen some improvement from roentgen ray treatment of morphea in an adult.

DR NELSON PAUL ANDERSON I do not know whether any one remembers a case of linear scleroderma distributed chiefly on one finger which I presented some years ago. I treated the child with bismuth subsalicylate and obtained great improvement. This youngster has considerable pigmentation in the involved area, and the disease itself may produce considerable atrophy. A



dermatologist might understand it, but any other physician might say that the changes were due to the irradiation. For this reason, if for no other, I recommend bismuth rather than roentgen ray therapy.

DR SAMUEL AYRES JR The father said that the boy has had almost constant colds, pneumonia twice and many sore throats.

DR ANKER JENSEN Some time ago Dr Robinson presented a patient with linear scleroderma of the forehead. He had treated it with a tissue extract, with satisfactory results.

**Lupus Erythematosus Hypertrophicus et Profundus (Bechet)** Presented by DR NELSON PAUL ANDERSON

J S, a white man aged 36, has had a lesion on the left side of his chin for the past twelve years. It started as a small red papule. He was seen eleven years ago by Dr Hiram Miller, of San Francisco, who made a diagnosis of a keratosis and treated it by curettement followed by cauterization with acid. The same treatment was given to the lesion seven years ago, since there had been recurrence by that time. Later it recurred again, and the entire lesion was excised three years ago. The excised tissue was submitted to a number of capable pathologists, including Dr Hamilton Montgomery. The most probable diagnosis was reported to be lymphoblastoma. Now the lesion is back again, recurring in the last three years on both sides of the linear scar of the previous excision. While in the Army the patient was seen by a Dr Vogel. Because of the likelihood of a lymphoblastoma he was given a medical discharge.

On examination there is an ovoid erythematous, thickened and infiltrated plaque on the left side of the tip of the chin. In its center is a linear depressed scar. The overlying skin of the lesion is erythematous and scaly, presenting a stippled appearance.

Microscopic examination of the tissue removed three years ago revealed the following changes: moderate hyperkeratosis, decided follicular dilatation and a slight acanthosis of the epidermis. Throughout the cutis and around the adnexa there is a pronounced focal infiltration of lymphocytes. This is especially evident about and beneath the dilated follicles.

DISCUSSION

DR M E OBERMAYER I remember Dr Irgang's paper on lupus erythematosus profundus, and I thought the sections were identical with those he described.

DR NELSON PAUL ANDERSON In 1936 the patient was treated by curettement followed by the application of an acid on the basis of a diagnosis of a keratosis. Some time later the entire lesion was excised, and the microscopic sections were made after that excision. For a while the excision was apparently successful, and the patient was inducted into the Army. Later two nodules recurred in the scar and the process then began to spread. A diagnosis of probable lymphoblastoma was made, and he was given a discharge from the Army. When he came in, I did not make a diagnosis of lupus erythematosus hypertrophicus et profundus of Bechet, but I thought the disease belonged in that group. I saw the slides three or four years ago and concurred in the opinion of lymphoblastoma. When the case is observed clinically and sections are then studied microscopically, the diagnosis of lupus erythematosus of a peculiar type is evident.

**A Case for Diagnosis (Colloid Milium?)** Presented by DR NELSON PAUL ANDERSON

R Z, a white woman aged 46, for the past fifteen years has suffered from an eruption on the face, neck and shoulders. It apparently started as small, hard, whitish papules on the forehead and gradually spread to involve the rest of the face, neck and the shoulders. No subjective symptoms are present. The pertinent past history reveals only a hypothyroidism for the past eight years, for which the patient takes 3 grains (0.19 Gm) of thyroid daily.

The examination reveals a diffuse erythema of the entire face, forehead, back of the neck and upper part of the chest. Scattered throughout these areas are countless small (pinpoint to pinhead sized), whitish, milium-like lesions. On incision the contents of such lesions are not easily expressed, as are the contents of true milia.

A punch biopsy was made to include three minute whitish papular lesions. In performing the biopsy, I found the skin to be very tough, both to the punch and to the suture needle. Histologic examination revealed no sign of colloid degeneration of the cutis.

DISCUSSION

DR M E OBERMAYER I was unable to make a diagnosis from the section, there was one cystic structure which did not have the features of a seborrhic cyst.

DR SAMUEL AYRES JR The patient says that her two brothers have the same sort of eruption, involving only the face and neck. It resembles a congenital milium-like defect of some sort.

DR NELSON PAUL ANDERSON I made a diagnosis of colloid milium and questioned it. This patient has a peculiar appearance with these pseudomilium lesions embedded in the skin. One can incise them and think that one is going to express a milium, but this does not occur. The eruption may be a peculiar reaction of exposed skin in a person with a sensitive type of skin. I feel sure that it is a peculiar degenerative process.

**NEW YORK DERMATOLOGICAL SOCIETY**

A BENSON CANNON, M D, *President*

GEORGE C ANDREWS, M D, *Secretary*

Feb 29, 1944

**Dermatomyositis** Presented by DR A BENSON CANNON

B V, a girl aged 13, was previously presented before the New York Dermatological Society on April 21, 1942, with a diagnosis of dermatomyositis, and is presented again today to show the remarkable improvement after therapy.

The treatment has consisted of ascorbic acid, 5 tablets (250 mg each) increased to 10 tablets daily, thyroid, ½ grain (0.03 Gm) three times a day, wheat germ, daily massage with cod liver oil, and exercise. She was given 200 r of unfiltered roentgen rays, at two week intervals, for a total of 600 r. After a four months' lapse, she was given another similar course.

The patient has slowly and progressively improved since the beginning of the treatment and is now able to do everything that a normal child can do, swimming, playing tennis, riding horseback and so on, and she has grown and developed normally. Spicules of calcium



have worked out of each one of the inflamed areas, and all hardness has disappeared, leaving the tissue surprisingly normal

## DISCUSSION

DR A BENSON CANNON Dr Imboden (who took the roentgenograms about a year apart) said that the last films showed about 75 per cent less calcium than did the films taken the year previously. The contractions in the legs and arms have almost disappeared

DR R H RULISON There has been a remarkable improvement, and I think Dr Cannon should be complimented. I will be glad to know what therapeutic agent he thinks was most effective

DR EUGENE F TRAUB I have in mind the patient I presented here a month ago with localized scleroderma on the leg, with open ulcers caused by the continual extrusion of calcium spicules. I requested suggestions for therapy, and one of the things I wanted to know was whether roentgen ray treatment was in order. I see that Dr Cannon used roentgen ray treatment in this case, and apparently it did no harm and might have helped to initiate the improvement.

DR GEORGE M LEWIS Will Dr Cannon review the symptoms for the purpose of differentiating calcinosis cutis and dermatomyositis?

DR A BENSON CANNON I cannot say whether anything I did was responsible for the remarkable improvement or whether she would have got better anyway. The fact does remain, however, that she showed improvement after her first visit and that this improvement has been steady and continuous. I am of the opinion that irradiation was most beneficial in her case, and my reason for giving it to her was that I have obtained remarkable results in the treatment of morphea by irradiation. I made every effort to build up the patient's general resistance. As for the differential diagnosis between dermatomyositis and calcinosis, I felt that the onset of the disease with swelling around the eyes was the most characteristic feature of dermatomyositis. Furthermore, the location of the deposits, with the changes in the parts, more nearly resembled dermatomyositis than calcinosis, and there was no involvement of bone or periosteum, as is often the case in calcinosis.

DR FRANK C COMBES One of the essential differential points between primary calcinosis and secondary calcinosis due to causes such as dermatomyositis is that in dermatomyositis there is evidence in the urine of destruction of muscle tissue, with the presence of creatine. I wonder if in this case there was a corresponding diminution of creatine in the urine with the clinical improvement of the patient.

DR A BENSON CANNON The patient showed an increase of creatine in the urine.

### Tinea Capitis (*Microsporon Audouinii*) Associated with Alopecia Areata Presented by DR GEORGE M LEWIS

M P, a housewife aged 31, is presented from the New York Hospital. Since the age of 7 years, she has had alopecia areata, affecting first the scalp and at about the age of 15 her eyebrows. There has usually been regrowth of hair within a few weeks or months, but growth on the back of the neck has been sluggish. She has never had hair on her arms and has only a few hairs on the legs and in the axillae. A brother of the patient also had alopecia areata.

For the past month, her 8 year old son has been treated for tinea capitis. When the patient complained of an itchy scalp, the scalp was examined. There are

several small areas of alopecia areata on the scalp and a larger area over the occiput, and the eyebrows are thinning. Clinically, tinea capitis would be difficult to diagnose with only mild scaling and few broken-off hairs. Under filtered ultraviolet rays, many small foci are readily detected.

## DISCUSSION

DR FRANK C COMBES It is always unusual to find tinea capitis in an adult, but I suppose that we have so much of this infection around now that it is only natural that a few adults should have it.

DR GEORGE M MACKEE I have not encountered many cases of ringworm of the scalp in adults. I remember 1 unusual case in which ringworm of the adult scalp was caused by *Microsporon lanosum* and 1 or 2 in which it was caused by *M. audouinii*, and another that I recall was an instance of the black dotted ringworm (due to *Trichophyton violaceum*), a very stubborn variety. No one knows why tinea capitis is so rare in adults. Its rarity has led to the suspicion of endocrine or hormonal imbalance as a causative factor, but I understand that attempts to overcome ringworm of the scalp in children by the administration of hormonal or glandular extracts have not been successful. At the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital we have been engaged in experiments concerning the pH of the scalp, and the results indicate that the pH of the scalp becomes higher with the advent of puberty, whereas the axillae have a lower pH. On the basis of those indications we think we have somewhat better results with topical remedies in diseases of the scalp if the vehicle is acidified.

DR GEORGE M LEWIS It does not impress me that the baldness is due to ringworm. The patient had alopecia areata for a sufficiently long time for it to be well established before she acquired the ringworm infection.

It will be of great interest to determine what effect estrogen will have in this patient. I think probably the immunologic phase has not been settled yet, because cutaneous tests are not a suitable method to determine whether a patient has reached an immune state. Determining whether a patient is or is not hypersensitive to trichophytin does not help in determining whether that patient is going to acquire ringworm infection. As yet there is no adequate way to answer that question. It is known that after a patient has ringworm infection for a certain length of time he gets well even without treatment. It may be simply a question of exposure to infection in childhood, and endocrine or hormonal imbalance may not have anything to do with it at all.

### Tuberculosis Cutis Serpiginosa Presented by DR GEORGE C ANDREWS

H S, a Negro girl aged 17, presented from Vanderbilt Clinic, complains of an eruption on the buttocks and in the groins which began at the age of 3 years. She states that the first symptom was a contracture of the left middle finger and that at about the same time a lesion developed in the left infraorbital region, which left a scar. Soon thereafter an eruption appeared on the buttocks. A biopsy was done by Dr Paul Gross at the New York Hospital for Joint Diseases. The biopsy showed tuberculosis cutis. The patient was sent to Seaview Hospital, she stayed for six months and left without the approval of her physicians.

The patient first came to the Vanderbilt Clinic on the day preceding this presentation, and the case has therefore not had a thorough study. Her eruption closely resembles that in a photograph in Ormsby's

textbook On both buttocks are atrophic scarred areas at the borders of which are linear gyrate symmetric lesions that extend symmetrically over the buttocks and into the groins

## DISCUSSION

DR GEORGE M. MACKEE The diagnosis appears to be correct The patient certainly does not have syphilis I think this used to be called tuberculosis cutis hypertrophica or tuberculosis cutis serpiginosa or lupus serpiginosus The histopathologic structure might be that of lupus vulgaris or simply that of tuberculosis Therapeutic results are uncertain The eruption is apparently too extensive for a plastic operation Perhaps some destructive method is indicated, but I suggest that a year or two of tuberculin therapy, combined with a high vitamin and low sodium chloride diet, general ultraviolet irradiation of the body, or heliotherapy, daily and local intensive ultraviolet irradiation with a water-cooled ultraviolet generator (Kromayer lamp) administered under pressure sufficient to dehematize the skin be tried The nonulcerative eruptions often yield satisfactorily to such treatment

DR FRED WISE I agree with the opinion expressed by Dr MacKee

DR FRANK C. COMBES I am interested to hear Dr MacKee mention tuberculin treatment, because that seemed to me to be applicable in this case This patient seems to offer considerable natural resistance to the tuberculous process as evidenced by the soft, pliable scar and by the intensely infiltrated tubercles in those areas at the borders where there is activity I should think tuberculin ointment used locally in addition to injections might be of some benefit

DR EUGENE F. TRAUB The local application of pyrogallol or some other escharotic might be valuable because of the narrow zone of active border present The central portion of the lesion is made up largely of scar tissue and can be left alone Even though the central scar tissue may not be entirely free of activity, if the marginal treatment is carried out without disturbing the scar tissue too much, a flare-up in the center of the lesion is not to be expected A method that might be employed in the absence of a Finsen lamp would be the application of the Kromayer lamp with pressure The radiation should be given in blistering doses, daily I have repeatedly seen surprisingly excellent results if this is persisted in with sufficient energy For this particular patient I advise against attempting to excise the entire area, I should cut out merely the active border This procedure would necessitate cutting through the scar tissue, however, and might light up new centers of activity Needless to say, while local measures are being carried out, all general measures used in cases of tuberculosis should be employed

DR GEORGE M. MACKEE I think the proper way to handle a disease of this type, if it is possible, is much the same as with any form of tuberculosis, such as pulmonary tuberculosis In other words, the regimen should include a liberal high caloric diet, outdoor life, heliotherapy, tuberculin therapy and administration of vitamins Also, ultraviolet irradiation under pressure with the Kromayer lamp should be applied locally I do not know whether in a Negro patient generalized ultraviolet irradiation would be of benefit I think that continuation of this form of treatment for eighteen or twenty months would be advisable Some of the nodules might have to be destroyed with pyrogallol or electrodesiccation Roentgen rays in small, safe therapeutic doses might also prove beneficial

## Mixed Nevus Presented by DR GEORGE M. LEWIS

D. C., a woman aged 59, a registered nurse, is presented from the New York Hospital She has had a birthmark affecting the right side of the neck as long as she can remember For the past two years there has been a noticeable increase in size The lesion is irregular in outline, is only slightly elevated and is comprised of both brown pigmented and purplish areas commingled A biopsy of a sample of the deep brown portion revealed an intraepidermal pigmented nevus

## DISCUSSION

DR GEORGE M. MACKEE I looked at the slides under the microscope, but unfortunately there was no satisfactory high power lens Under the low power the picture looked like an intraepidermal nevus, one that is not dangerous I should either leave it alone or excise it

DR FRED WISE I believe excision and skin grafting would be a simple procedure and would promptly rid the patient of her worries

DR EUGENE F. TRAUB This patient was presented with a diagnosis of a mixed type of nevus, and inspection of the nevus suggested that part was deeply pigmented and other portions were softer and apparently inflammatory or vascular On inspection of the slide for just a few minutes I did not see any vascular element microscopically, possibly because the small section taken for biopsy did not include the various elements of the lesion The section, however, did show what seemed to me to be a typical junction type nevus, the activity being at the epidermal-dermal border If my interpretation of the slide is correct, this nevus might be a precursor of a malignant melanoma Dr Lewis mentioned that the slide was reported as showing cellular nevus If I understand that term correctly, it would apply to any lesion in which nevus cells are found This, of course, is a loose and general classification and does not indicate much about the true character or potentialities of the nevus In this particular instance it would give no clue as to whether this was a benign or a possibly premalignant or an already malignant lesion Judging by the slide, the nevus seems benign at present, but since it shows a tendency to increase in size, I believe this lesion to be potentially dangerous and suggest that it be excised and that skin be grafted There can be no risk in removing the lesion at the present time, provided the removal is thoroughly and adequately done, and it might prevent the development of a future melanoma

DR JOHN C. GRAHAM I should have this lesion excised It seems to me that it is potentially malignant

DR R. H. RULISON I agree with Dr Wise I think the patient is more worried about this than she should be and that therefore the lesion should be excised and skin grafting done

DR GEORGE M. MACKEE I could not make out a junction nevus under the microscope, but that may be because I could not use the high power lens It makes a great difference, as Dr Traub has said, whether this is an intraepidermal or a junction nevus If it is a junction nevus, it is still benign, but I should have it excised because of her age She is in the cancer age now

DR GEORGE C. ANDREWS It does not seem fair to judge the nature of the whole lesion just from a small specimen taken for biopsy After all, that lesion is 3 to 4 cm in diameter, and this specimen covers only a few millimeters of one part of the lesion We do not

know what is going on in the rest of the lesion I am therefore in accord with those who think this lesion should be thoroughly excised

DR GEORGE M LEWIS The presentation diagnosis was based clinically on the fact that there are different hues of color in the lesion Part of the lesion certainly has a vascular tint clinically The slide I examined showed no evidence of a junction type nevus

**Lichen Planus Hypertrophicus of the Thigh, Associated with Lichen Planus of the Scrotum**  
Presented by DR FRED WISE

F P, a man aged 44, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb 24, 1944, because of lesions

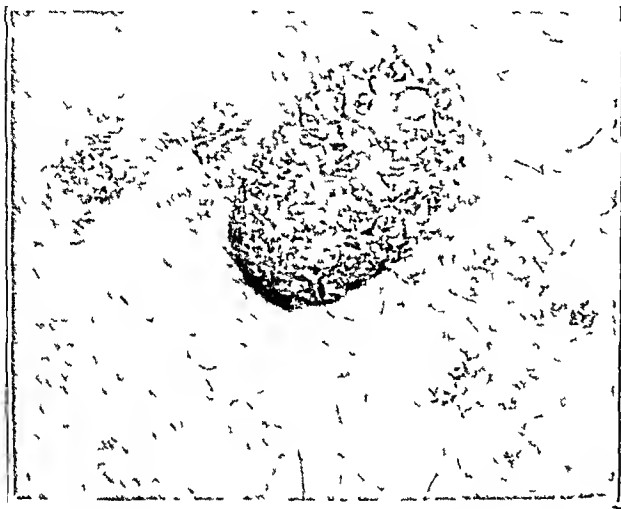


Fig 1—Lichen planus hypertrophicus

of four years' duration Itching began only a year ago He gave a history of having had sumac or oak poisoning three months before the appearance of the present eruption, for which he received subcutaneous injections for three months The rash was erythematous and blotchy, but not raised, and involved the trunk and extremities All the lesions underwent regression at that time except one area on the outer surface of the left thigh, which is the location of the present elevated lesion Within three weeks after its appearance, it became raised and gradually larger It assumed its present form within one and one-half years

On the middle of the outer surface of the left thigh is a well defined oval plaque 3 by 2.5 cm in size and raised about 5 mm It has a dull purplish red color and is painless and nontender The surface of the plaque is rounded and rough, covered with hard pinhead-sized to barley-sized keratotic plugs This plaque is surrounded, within an area the size of a palm, by several similar pinhead-sized to large-pea-sized satellite lesions Distributed on the scrotum are many match-head-sized to pea-sized, soft, smooth, purplish nodules, most of them discrete but some coalesced to form bean-sized plaques Some of the nodules have concave surfaces There is only a faint suggestion of the presence of fine threadlike and circinate lesions of lichen planus in the oral mucosa There are fairly well defined areas of dusky erythema on the outer surfaces of both forearms These were attributed to contact dermatitis due to gasoline

The routine laboratory tests showed nothing abnormal A biopsy of a section from the large, raised

plaque was done by Dr Charles F Sims, and the diagnosis was hypertrophic lichen planus The section was described as follows The epidermis was extremely and irregularly acanthotic It was covered in part with a well defined but verrucous horny layer The granular layer was increased at several points Underneath these points there was a liquefaction of the basal cell layer Directly beneath the latter areas there was a bandlike infiltration composed for the most part of small round and wandering connective tissue cells

DISCUSSION

DR PAUL E BECHET Most of the lesions are typical of lichen planus hypertrophicus, but I am not so sure of the tumor on the thigh While I know that actual tumors can occur in this dermatosis, they must be rare The disease is so recalcitrant to treatment that an excision of the tumor would not only give excellent cosmetic results but also furnish material for further histopathologic work in order to eliminate the least possibility of a new growth not related to the disease

DR GEORGE M MACKEE I think the lesion on the thigh is lichen planus hypertrophicus It is interesting here, as it is with all diseases, to think what one would call a certain aberrant lesion if there were no concomitants I doubt that any of us would have thought of lichen planus if there were only that one lesion, but lichen planus can produce unusual lesions It can produce hypertrophic lesions and also tumor-like lesions I agree with the diagnosis



Fig 2—Lichen planus hypertrophicus

**A Case for Diagnosis (Lupus Erythematosus?)**  
Presented by DR EUGENE F TRAUB

P W, a man aged 45, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital About two and one-half years ago he noticed a firm, flat, slightly elevated dull red lesion about 1/2 inch (1.3 cm) in diameter on the medial aspect of the calf of the right leg The lesion was smooth, dry, nonscaly and at times slightly pruritic Round at first, the lesion later became oval and reddish purple There was no pain or tenderness and no history of trauma to the leg

Six to eight months later, the patient noticed a group of lesions on the tip of the nose, of which two or three were discrete and the remainder confluent, yellowish red, raised, round and occasionally pruritic, the entire group having a diameter of about  $\frac{1}{4}$  inch (0.6 cm). The lesions never at any time disappeared completely. At times the lesions were exudative, at other times they were crusted. Topical medication was ineffective. In March and April 1943 the patient received six to eight roentgen ray treatments to the nose from a local physician. No immediate response was seen, and within a few weeks he noticed exacerbation with spreading. This has been going on for the past year.

On December 22 the patient first appeared at the clinic. There was a nodular, reddish purple denuded exudative area on the internal aspect of the right leg. The tip of the nose presented an ill defined erythematous, slightly violaceous area, denuded, moist and irregularly covered with thin superficial yellowish crusts. The periphery showed atrophy and telangiectasia. The lesions oozed continually.

A biopsy of the lesion on the leg revealed dilated blood vessels with chronic inflammatory response. For the first biopsy of the lesion on the nose insufficient tissue was taken. Results of the second biopsy suggested a diagnosis of lupus erythematosus.

Examination at present shows a lesion on the right leg about 1 inch (2.5 cm) in length and  $\frac{1}{4}$  inch (0.64 cm) in width, purplish red, flat, level with the skin, soft, smooth, dry and nonscaling, showing previous biopsy scars. The tip of the nose presents an irregularly circumscribed reddish brown area about 1 inch (2.5 cm) in diameter, the surface of which is roughly granular, moist and spotted with a thin yellowish slightly adherent crust. The lesion is firm, not painful and not tender. The sides of the nose are reddish purple, and show some comedos, dilated follicles and a few fine telangiectases. The progress of the lesion at all times has been slow, it has shown the greatest increase in size during the past month.

#### DISCUSSION

DR GEORGE M LEWIS I suggest that a culture be made for fungi with the thought of chromoblastomycosis in mind. That diagnosis might be inferred from the clinical appearance.

DR FRED WISE The only suggestion I can make in regard to therapy is that the affected area be destroyed by electrodesiccation.

DR GEORGE M MACKEE I think Dr Lewis' suggestion is good, but clinically I will hazard a guess that this is erythroplasia. What to do for erythroplasia I do not know, except to attempt complete destruction. Roentgen rays and radium seem to be useless, and even complete destruction is difficult, but if the patient would allow it, I would treat this lesion with electrocoagulation. However, the diagnosis should first be established unequivocally.

DR EUGENE F TRAUB The reason a third biopsy was performed was that repeated suggestions were received at the staff conference and from members of the clinic who felt that this must be a case of erythroplasia or Bowen's disease, but none of these suggestions could be substantiated microscopically.

DR GEORGE M MACKEE This lesion has been present for a long time. It began as a small lesion, probably a macule or papule no larger than a pinhead, and it has spread peripherally. It is progressive and continuously exudative. These characteristics constitute the picture of erythroplasia. Until the histopathologic study

disproves the diagnosis, I prefer to consider it erythroplasia.

DR GEORGE C ANDREWS I suspect that Dr MacKee is right, in spite of the three biopsies that have been done. One other possibility that entered my mind was dermatitis artefacta. I doubt that diagnosis, but it has to be considered.

DR R H RULISON I, too, was going to suggest the diagnosis of dermatitis artefacta. This man has used lacquer and dye on his hair, and he might also conceivably have produced this lesion artificially.

DR FRANK C COMBES Dermatitis artefacta is extremely rare on the eyelids, the nose and the genitals.

DR EUGENE F TRAUB It was my opinion that the disease might be erythroplasia or Bowen's disease, but biopsy did not bear this out. Either the material was taken from the "ringworm" section and was not characteristic of the lesion, or this diagnosis must be excluded. The treatment that has been suggested by Dr Wise is exactly what I have been wishing to undertake for some time, namely, to destroy the lesion, leaving only superficial scar tissue. However, without some backing such as that given by the members today, I did not like to undertake this type of therapy for this particular patient. The man does not give me the impression that he is a malingerer. He is a musician and, to hold his job, must be careful of his appearance. He has not had a sealed dressing at any time. A diagnosis of pemphigus has been considered, but the duration of the lesion of almost two years and the location only on the nose seemed decidedly against such an idea.

DR GEORGE M MACKEE Another possibility is the Senear-Usher syndrome.

DR EUGENE F TRAUB If one wishes to reconcile the histologic suggestion of lupus erythematosus, one might consider the diagnosis of a Senear-Usher type of pemphigus or a bullous lupus erythematosus. Otherwise, from the clinical appearance, I cannot see any reason for the diagnosis of lupus erythematosus.

#### Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi with Sarcoid-Like Changes in the Lymph Nodes Presented by DR FRED WISE

M S, a Russian Jew aged 64, was referred by Dr Ben Kanee for demonstration. He was admitted to the New York Post-Graduate Medical School and Hospital on Feb 18, 1944, because of lesions of two years' duration. He has had a chronic cough for years. During the past one and one-half years he has lost 68 pounds (31 Kg) in weight. He also complains of loss of appetite, weakness, nocturia and frequency of urination for the past six months and of severe dyspnea on exertion for the past six weeks.

About two years ago the patient noticed a dime-sized, nonpruritic blister on the inner aspect of the left heel. Similar lesions developed within a year on the inner surface of the left sole and big toe. A year ago the left foot and ankle became swollen. Six months ago, new lesions appeared on the nose, the hands, the fingers and on the right foot. All these lesions have persisted since. He was treated a year ago at the Hackensack Hospital in New Jersey with a course of roentgen irradiations to the sides of the neck, the axillas and the inguinal regions and with more roentgen irradiations on the inguinal regions six months ago at the Englewood Hospital. He received whirlpool baths three times weekly for the feet, which were edematous.

On the left cheek is a raised globular verrucous lesion the size of a small pea which has been present for three

months and resembles a basal cell epithelioma. On the tip of the nose is an arciform, raised, smooth purplish infiltrated nodule. On both palms and fingers are similar circumscribed raised purplish infiltrated plaques and superficial beginning lesions. There are similar variously sized plaques, infiltrated, raised and superficial, on the outer and inner borders of the sole of the left foot and on all the surfaces of the toes. There is a palm-sized, superficial infiltrated plaque on the outer surface of the right heel, with smaller plaques on the inner aspects of the sole and on the first and second toes. There are three isolated pea-sized purplish lesions on the anterior aspect of the left leg. The left foot and ankle are edematous. Small lymph nodes are palpable in the anterior cervical and axillary areas.

The patient appeared emaciated, he was in bed and in apparent distress. There was a pronounced deviation of the trachea to the right. The apex beat was in the sixth interspace. There were no murmurs audible. The blood pressure was 112 systolic and 60 diastolic. Crackling rales were heard over both bases. The prostate gland was normal.

The routine laboratory tests, including the routine chemical tests of the blood, revealed nothing abnormal. The sedimentation rate was 39 mm per hour (normal for males is 10 mm per hour by the Westergren method). The vitamin C content in the blood plasma was 0.1 mg per hundred cubic centimeters (normal 0.7 to 1.4).

The reports on the biopsies of two different lymph nodes, examined at the two aforementioned hospitals, gave the diagnosis of Boeck's sarcoid. A section of skin taken at the New York Post-Graduate Hospital and examined by Dr Charles F. Sims showed the histologic structure of Kaposi's sarcoma.

#### DISCUSSION

DR PAUL E. BECHT: I agree with the diagnosis of Kaposi's sarcoma as far as the subcutaneous lesions are concerned. The histologic structure of the lymph nodes is interesting. It should be investigated further, and I hope that Dr Wise will make a further report on that at a later meeting, to determine whether the structure is sarcoid or not.

DR FRANK C. COMBES: I agree with the diagnosis as presented. A number of years ago Dr Greco in Buenos Aires reported inclusion bodies in several cases of Kaposi's hemorrhagic sarcoma. I have encountered only 1 case since then, though I have looked for instances. It would be interesting in this case to make blood smears and see if such bodies can be found. Dr Greco sent me some of his smears. Dr Symmers and I both looked at them, but we were not impressed.

DR GEORGE M. MACKEE: I am sorry that I did not see these slides at the clinic. With the available microscope one can use only the low power. I cannot interpret this slide well, but I do not feel certain that the cells in the lymph node are epithelioid cells. I think it requires further study to establish what they are. They may be sarcoma cells.

DR EUGENE F. TRAUB: There seems to be a general agreement with the diagnosis in this case, but I do not believe that the lesions in the mouth were mentioned. There appear to be two purplish red nodules on the left anterior pillar and on the adjoining hard palate. Lesions in the mouth are probably not as uncommon as is the lesion on the nose, but nevertheless it is interesting to mention them.

DR GEORGE M. LEWIS: There is a lesion on the forehead which was not mentioned in the history.

DR BEN KANEE (by invitation): We are making attempts to obtain the original blocks of the biopsy specimen of the lymph nodes, and further studies of these will be made. I am interested in knowing whether any of the members had seen sections of lymph nodes in Kaposi's disease and whether the histologic picture is the same as that found in the cutaneous lesions, or whether it is entirely different. One other feature of this case is that the patient has lost 68 pounds (31 Kg) in weight in the past two years and complains of general weakness and anorexia. The presumption is that this man may have visceral involvement. A series of roentgenograms of the gastrointestinal tract have been made, but no evidence of pathologic changes was noted.

DR GEORGE M. MACKEE: I have seen histologic specimens of Kaposi's sarcoma from every part of the body, including the lymph nodes, and the histologic picture is always the same, no matter from what part the specimen is obtained. For this reason there seems to be a consensus now that there is no metastasis in Kaposi's sarcoma. It is a multicentric development, and no part of the body is immune. Another interesting feature of this case is the lesion on the nose. It reminds me of a patient Dr Wise had many years ago, whom I think he described in a published report, in whom the initial lesion was on the tip of the nose.

DR FRED WISE: I stressed the point that neither Dr Jessner nor Dr Richter was able to confirm that there were epithelioid cells in the section of the lymph node without further studies and staining. I am sorry that I did not see the lesions in the throat which were mentioned.

#### Lupus Erythematosus of Occupational Origin Presented by DR R. H. RULISON

S. P., a man aged 59, with no history of previous important illnesses or cutaneous disease, had been employed for eight months as a maintenance mechanic in a plant where aluminum is smelted. In August 1943 he had to make repairs on a hot aluminum pot and during this work was exposed to intense heat. Within twenty-four hours his face and ears became hot, red and tender, and the upper halves of both ears became swollen. He received appropriate treatment in the first aid station of the plant, and within two or three days his face was normal. The ears remained swollen and sore and after ten days peeled. A scaling, dry itching dermatitis developed on the upper parts of both ears, the most severe eruption being on the left ear. A small rounded patch of similar dermatitis also appeared on the prominent part of the left mastoid region. The eruption remained intractable to treatment and is still present. There has been continued, severe itching.

On January 31, 1944, Dr G. F. Machacek made the following report on a biopsy of material taken from the patch on the left mastoid region: "Sections of a piece of skin disclosed epidermis which was somewhat atrophic and had undergone a slight hyperkeratosis with keratin plugging of follicular infundibuli. The cutis showed basophilic degeneration of the collagen bundles, particularly in the upper strata. Foci of mononuclear infiltration were present, the cells appearing to be lymphocytes. The changes which were noted were probably due to actinic irritation of the skin and not incompatible with the diagnosis of lupus erythematosus. It is my opinion, however, that the lesion is an actinic dermatitis."

Dr Frank C. Combes saw this eruption recently and considers it lupus erythematosus caused by exposure to intense heat. The case is believed to be interesting.



because of its industrial origin, which makes it a compensable condition, and because the precipitating cause was intense heat rather than ultraviolet rays

The presentation diagnosis is lupus erythematosus of the ears of industrial origin, caused by exposure to heat only

## DISCUSSION

DR JOHN C GRAHAM I agree with the diagnosis of lupus erythematosus. It is unusual to have it develop as a result of exposure to heat, but I can see no reason why it cannot.

DR EUGENE F TRAUB This being the first of a series of such cases that may appear and the medicolegal angle being involved, it is rather important to try to settle whether heat is a precipitating factor in lupus erythematosus. In this case the time of onset appears to have been definite—directly after the exposure to intense heat. Of course, in any history a patient is inclined to date the onset of his trouble by some outstanding event, and there is always the question of coincidence which must be taken into consideration. The point I make is that when a patient has an accident or is exposed to a certain thing and then a disease follows one must be sure in one's decision as to whether there was an association between the two events.

DR PAUL E BECHET I agree with the diagnosis. The lesions are typical of lupus erythematosus, despite the fact that those on one ear are somewhat masked by dermatitis. The question whether heat would be a precipitating factor is one with which I have had no experience. I have time and time again observed cases of lupus erythematosus precipitated by actinic light but never by heat alone.

DR FRANK C COMBES I saw this patient in consultation with Dr Rulison. I think he has classic lupus erythematosus. Approximately 15 per cent of instances of this disease are precipitated by exposure to the actinic rays of the sun. However, radiant energy of longer wavelength is not necessarily eliminated as a factor capable of producing similar injury to the skin. The intense heat to which this man was exposed has traumatized the skin, producing vascular changes. It is common for lupus erythematosus to follow trauma, and I think that is what happened in this case. The heat to which he was exposed was extreme enough to melt aluminum.

DR JEROME KINGSBURY I do not feel there is sufficient clinical evidence in this case to warrant a definite diagnosis of lupus erythematosus. The left ear, to my mind, presents the appearance of a simple chronic dermatitis. On the right ear there is a suggestion of lupus erythematosus, but I do not think that diagnosis can be made positively.

DR FRED WISE I thought lupus erythematosus was the most likely diagnosis, chiefly on account of the small maculopapular lesions in front of the ear. I do not believe that heat itself is a precipitating agent in the causation of lupus erythematosus. If it were, those who have been practicing dermatology for many years would have encountered such cases before, especially among such workers as stokers on board ships or men working in vats in the fuel oil and gasoline industry. One would expect to encounter many cases of lupus erythematosus due to exposure to intense heat among such workers. Although I agree with Dr Combes that the precipitating agent may be almost any trauma, I do not believe heat in itself is a factor in the causation of lupus erythematosus.

DR GEORGE M MACKEE It looks like lupus erythematosus to me. The right ear shows thickening, hyperkeratosis and follicular plugs. There is a patch of typical lupus erythematosus on the right cheek. I admit that the lesion on the left cheek does not look like lupus erythematosus. I agree with Dr Combes that lupus erythematosus apparently can be precipitated in various ways. Actinic light is one precipitating factor which is well known. There is no good reason to believe that actinic rays are always to blame in these cases. In sunlight there are, after all, not only the actinic rays, but also the infra-red rays and the rays of the visible spectrum. Like Dr Combes, I have seen lupus erythematosus precipitated in other ways—by acid burns, for instance. I have seen it develop in a vaccination scar. While I have never encountered a case of lupus erythematosus which was apparently precipitated by heat, it may be possible, especially if the heat is radiant.

DR GEORGE C ANDREWS I have little to add to the discussion except that I have frequently seen, and others have too, patients with lupus erythematosus whose eruptions were made worse, or whose attacks were made much more severe, by exposure to heat. On very hot days during the summer, even though patients stay indoors out of the sunlight, their conditions are much worse. I have had that opinion for years about the effect of heat.

DR GEORGE M MACKEE I do not think Dr Wise's argument is convincing. As he says, there are many people working in intense heat in whom lupus erythematosus does not develop. The same thing is true of farmers and sailors who work in the sun all day, as well as of all the people who go in for the fad of sun bathing. Only a few of these have lupus erythematosus. This case involves a compensation, and one should be careful what is stated. Such records may get into the hands of insurance companies or lawyers. It has not been proved that the eruption was precipitated by heat. I simply say that heat may possibly precipitate lupus erythematosus. Unless one can say that it cannot be precipitated by heat, the patient may be compensated, because the workmen's compensation law grants the insured the benefit of the doubt.

DR R H RULISON I did not say this lesion was caused by exposure to heat. I said that it was precipitated by the heat. There must be some predisposing factor or focus of infection before a precipitant can bring on an attack of lupus erythematosus. Therefore, I think it would probably be wrong to say that this man's lupus erythematosus was caused by exposure to intense heat. We should say that it was, or rather might have been, precipitated by exposure to intense heat. The chronology is fairly well established. He got a severe erythema from the heat to which he was exposed and was treated in the first aid station. The eruption on the face cleared in three to four days, but the condition of the ears became worse.

#### Generalized Granuloma Annulare Reported by DR GEORGE C ANDREWS

Mrs J J, aged 60, was presented before the New York Dermatological Society on Jan 25, 1944, with an extensive eruption of granuloma annulare.

The patient has gone back to California, and the eruption has cleared entirely. The section was shown to Dr Wilbert Sachs, as well as examined by Dr G F Machacek, and they agreed that it was granuloma annulare and that there was no sign of syphilis in the section.

The eruption cleared with roentgen therapy.



## Book Reviews

**Modern Clinical Syphilology** By John H Stokes, M D, Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, Director, Institute for the Control of Syphilis, University of Pennsylvania, Herman Beerman, M D, Sc D (Med) Assistant Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, University of Pennsylvania, and Norman R Ingraham Jr, M D, Assistant Professor of Dermatology and Syphilology, School of Medicine, University of Pennsylvania. Third edition, reset. Price, \$10. Pp 1,332, with 911 illustrations. Philadelphia and London W B Saunders Company, 1944

The third edition of Stokes's classic textbook on syphilis now also bears the names of Beerman and Ingraham, both assistant professors of dermatology and syphilology at the University of Pennsylvania. In the preparation of this encyclopedic work they also had the assistance of eight instructors in the same institution. With this array of talent it is not too much to expect a superb book on the diagnosis and treatment of syphilis, which is up-to-date, readable and accurate. The reader will not be disappointed in his expectations.

The authors wisely decided to publish the book in one volume, which is the only practical form for the student or practitioner. A book in two volumes would have been purchased mainly by libraries and dermatosyphilologists. To produce a single volume on syphilis, containing 1,332 pages (including the index) and many illustrations, the authors must necessarily curtail the size of the text in one way or another, hence they have used a rather large amount of fine print and have omitted extensive bibliographic references.

The authors state that 75 per cent of the text has been rewritten and that the chapters on penicillin and syphilis as related to public health and military medicine are new. Serologic reactions have been given full attention, especially the troublesome biologic false positive ones. Cutaneous aspects of the disease are profusely illustrated, and throughout the book are scattered 453 "thumbnail summaries," which constitute a favorite and useful method of teaching of the senior author. A valuable feature for experts in syphilis is the inclusion in fine print of histories of cases difficult for diagnosis or treatment.

Although the term "modern" appears in the title, it is admitted that in the next ten years the arsenical treatment of the disease may be obsolete. At present, however, the entire volume is certainly modern and up-to-date.

Minor criticisms can always be made against any large textbook, though there is little this reviewer can find to criticize. The improper term "heredo-syphilis" is mentioned in quotations as a synonym of prenatal syphilis. It would thus appear that the authors disapproved of the term "heredo-syphilis," although it is frequently used in the course of chapter XXI in headlines of sections and captions for illustrations. The term "congenital syphilis" is mentioned only in quotations

although in the introduction it is stated that the disease is now largely called "congenital syphilis."

The general appearance of the volume is attractive, thin glazed paper having been used throughout.

The authors have done a magnificent piece of work in writing this book, which should be in the possession of every one who is interested in syphilis, including every dermatosyphilologist.

**Paradenitinfitis o enfermedad de Nicolas-Favre o linfogranulomatosis venérea** By Jose May M D. Price, not given. Pp 134. Montevideo, Imprenta "El Siglo Ilustrado," 1943.

The author of this monograph is a well known authority on lymphogranuloma venereum, having published in 1940 a monograph with interesting observations. This new book is a summary of a series of lectures given at Buenos Aires during the commemoration of the thirty-fifth anniversary of the foundation of the Argentinean Dermatological Society.

In this book the author reviews the most recent developments in the clinical picture of the disease. There are also interesting discussions about the diagnosis, epidemiology and treatment. He has done a patient work gathering together from widely scattered sources most of the articles published on the subject. The bibliography consists of seventy-eight Uruguayan references and two hundred and seven from other countries.

The author describes in detail the characteristics of the association of lymphogranuloma venereum with other venereal diseases, basing his conclusions on many original observations. He also discusses the possible lymphogranulomatous origin of induratio penis plastica, Dupuytren's contracture, regional edema of the penis and the ocular changes observed in lymphogranuloma venereum already studied by him and reported on in many recent publications.

Lymphogranuloma venereum is also considered as a possible etiologic factor in some cases of Buerger's disease, arteritis obliterans, tabes, otosclerosis and epilepsy. The amount of evidence is, however, by no means conclusive, as it is often based on an occasional positive Frei reaction. Although this test is highly specific, its positive result is not a definite proof that the disease in question is due to the virus of lymphogranuloma venereum. In spite of this objection, the problems presented in the book are highly interesting and require careful consideration. This work is a challenge to all persons interested in the subject.

**An Annotated Bibliography of Medical Mycology 1943** By S P Wiltshire, C Wilcocks and J T Duncan. Price, not given. Pp 32. Kew, Surrey. The Imperial Mycological Institute, 1944.

This booklet lists two hundred and eighteen articles published during 1943 in various medical journals, all dealing with some phase of medical mycology. In one hundred and four instances a brief abstract is appended. Separate appendices follow, listing both authors and subject matter in alphabetical order.

The value of this bibliography to students and workers in this field is self evident.

## HEMANGIOENDOTHELIOMA OF THE SKIN

MARCUS RAYNER CARO, M.D., AND C. H. STUBENRAUCH, JR., M.D.

CHICAGO

For nearly all types of tumors of the skin it is possible to make the correct diagnosis and to establish the prognosis from the histologic examination of a specimen. Such relative accuracy of results of laboratory procedure, however, does not hold true for tumors of the blood vessels. Examples are occasionally seen of tumors which histologically show great cellular activity but which follow a benign course. More often, however, one encounters vascular tumors which seem histologically benign but which in time metastasize and eventually cause death.

This frequent discrepancy between the histologic changes and the clinical course has made it difficult to establish an acceptable classification of tumors of the blood vessels. A simple grouping,<sup>1</sup> based on a consideration of both clinical and histologic features, would divide such tumors into (1) hemangiomas, which are benign clinically and histologically, (2) hemangioendotheliomas, in which histologically there is proliferation of endothelial cells and clinically a gradation from a benign to a malignant course, and (3) malignant endotheliomas, in which malignancy is evident both clinically and histologically. The term hemangioendothelioma was first used by Mallory.<sup>2</sup> At one time this name was used to designate many tumors which have since been identified as belonging to other groups. Ewing<sup>3</sup> accepted as a hemangioendothelioma "a slowly growing tumor of the skin or subcutaneous tissue, occurring chiefly in children in which there is a nearly diffuse growth of

endothelial cells with imperfect formation of capillaries (hemangioma hypertrophicum cutis)." Stout<sup>4</sup> stated that no tumor should be considered a hemangioendothelioma unless the following two features are present: "first, the formation of atypical endothelial cells in greater numbers than are required to line the vessels with a simple endothelial membrane, and, second, the formation of vascular tubes with a delicate framework of reticulin fibers and a marked tendency for their lumens to anastomose." In spite of the narrowing criteria for accepting the diagnosis, there have been several reports in recent years of cases which seem to qualify for the diagnosis of hemangioendothelioma.

Pulford<sup>1</sup> reported a fatal case of hemangioendothelioma in a woman who had a recurring tumor of the breast. The pathologic interpretation of an early specimen was hemangioma. The later pathologic findings were those of hemangioendothelioma, both in the recurrence at the original site and in the metastases. He selected 200 cases of neoplasms of the blood-lymph-vascular system in which there was adequate material for histologic study. These cases included 183 of angioma, 9 of angioendothelioma and 8 of endothelioma. On the basis of this study, the author expressed the opinion that "angiomas, while usually benign, are potentially malignant endotheliomas, there is an intermediate stage between these two represented by the angioendothelioma which is relatively benign but definitely malignant, and malignant endotheliomas of the blood-lymph-vascular system exist as a pathologic entity."

Livingston and Klemperer<sup>5</sup> reported a fatal case of malignant angioma of the scalp (case 2) with apparently benign histologic features. Their histologic examination revealed unripe mesenchymal tissue as a constituent of the tumor,

From the Department of Dermatology, University of Illinois College of Medicine, service of Dr. Francis E. Senechal.

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 20, 1944.

1. Pulford, D. S., Jr. Neoplasms of the Blood-Lymph-Vascular System with Special Reference to Endotheliomas, *Ann Surg* 82:710, 1925.

2. Mallory, F. B. The Results of the Application of Special Histologic Methods to the Study of Tumors, *J. Exper. Med.* 10:575, 1908.

3. Ewing, J. Neoplastic Diseases, ed. 4. Philadelphia, W. B. Saunders Company, 1940, p. 344.

4. Stout, A. P. Hemangio-Endothelioma. A Tumor of Blood Vessels Featuring Vascular Endothelial Cells, *Ann Surg* 118:445, 1943.

5. Livingston, S. F., and Klemperer, P. Malignant Angiomas, *Arch Path* 1:899 (June) 1926.

explaining the malignant nature of this type of neoplasm

Downing and Mallory<sup>6</sup> presented a case in which an invasive hemangioendothelioblastoma developed on the left side of the neck after an injury by an exploding shell

Markowitz<sup>7</sup> reported a fatal case of malignant hemangioma of the wall of the chest following a local injury. Necropsy showed metastatic vascular tumors in which the cells were invasive but showed no anaplasia

Geschickter and Keasbey<sup>8</sup> discussed benign and malignant tumors of the blood vessels. They excluded from the group of malignant vascular lesions all tumors except metastasizing hemangiomas, primary angiosarcoma of the liver in infants and Kaposi's hemorrhagic sarcoma of the skin

Robinson and Castleman<sup>9</sup> reported a fatal case of a hemangioma of the breast which was benign histologically but which produced definitely malignant metastases

Sweitzer and Winer<sup>10</sup> reviewed the literature and formulated restrictions for the establishment of the diagnosis of hemangioendothelioma. They reported 6 cases in which the tumors were diagnosed histologically as belonging to this group. While trauma was a factor in the causation in 3 of these cases, in no instance did the authors record a change from a benign angioma which had been present for some time into a hemangioendothelioma. Treatment was carried out by excision, destruction by actual cautery or electrocoagulation and irradiation with radium and high voltage roentgen rays. In 5 of the cases there was freedom from recurrence at the time of reporting.

Stout<sup>4</sup> reported 18 cases of hemangioendothelioma, in 6 of which the lesions originated in the skin and subcutaneous tissues. The course of the disease in these cases confirmed the malignant nature of the tumors. At the time of writing 10 of the patients had died, with metastases, and only 4 were known to be free from recurrence, 1 of these for a period of more than five years.

6 Downing, J. G., and Mallory, G. K. Cavernous Hemangioma and Trauma, *Arch. Dermat. & Syph.* **22** 414 (Sept.) 1930

7 Markowitz, B. Malignant Hemangioma, *Am. J. Clin. Path.* **5** 333, 1935

8 Geschickter, C. F., and Keasbey, L. E. Tumors of Blood Vessels, *Am. J. Cancer* **23** 568, 1935

9 Robinson, J. M., and Castleman, B. Benign Metastasizing Hemangioma, *Ann. Surg.* **104** 453, 1936

10 Sweitzer, S. E., and Winer, L. H. Hemangioendothelioma, *Arch. Dermat. & Syph.* **34** 997 (Dec.) 1936

# REPORT OF A CASE

J. S. B., a white American man, 75 years old, was first seen on Oct. 21, 1943. Fifteen months previously he had bumped his head accidentally. No bleeding occurred at the time of injury, and there was no break in the skin, but about one month later a purplish discoloration was noticed at the site. About six months after the lesion on the scalp was first noticed, it began to spread appreciably by peripheral extension. During the following eight months the forehead, eyelids, cheeks and left side of the jaw were involved in succession. At no time were there any subjective symptoms or fever.

Physical examination revealed a well nourished man whose general health seemed to be good. The appearance of the head was striking (fig. 1). On the frontal and parietal regions of the scalp, extending across the hair line over the forehead, temples, eyelids and cheeks and behind both ears was a diffuse reddish brown discoloration. On the right side of the face the tragus marked the level of the lower border of the patch, while on the left side there was a wide band that extended downward in front of the ear and below it to fuse with the postauricular discoloration. Nowhere was the patch sharply outlined, and beyond the indistinct border were many dark red punctate telangiectases and petechiae. Within the patch much of the redness could be removed by pressure with glass, leaving a residual brown pigmentation. The skin on the forehead was slightly thickened, while over the left temple and eyebrow it was more puffy. The lids of the right eye were swollen and infiltrated, but the eye could be opened without difficulty. The lids of the left eye, however, were swollen completely shut, and they could not be separated. Both lids were firmer than normal, were of a bluish red color and had a papillary surface, while the lower lid formed a prominent mass that projected slightly over the cheek. At the left angle of the jaw there was a scar resulting from a boil that had been present four years previously. At this site the tumor was hypertrophic and spongy, and it could not be completely reduced by pressure with glass. Inside the left cheek near the corner of the mouth there was a small bluish red, hypertrophic, soft nodule. The left tonsil was enlarged and nodular, but it was not abnormal in color.

The blood pressure was 155 systolic and 90 diastolic. The heart was enlarged to the left. The lungs were clear. The edge of the liver was firm, round and not tender, and it extended 1 inch (2.5 cm.) below the costal margin. The spleen was not palpable. There was no lymphadenopathy. Roentgen examination of the skull showed nothing abnormal. On ophthalmoscopic examination the right fundus was found to be normal except for moderate vascular sclerosis. The left fundus could not be visualized because of the swelling of the eyelids. A specimen for biopsy was taken from the left temple, and the histologic changes will be described later.

Urinalysis showed no pathologic conditions. The Wassermann and Kahn reactions of the blood were negative. Chemical examination of the blood showed dextrose, 81 mg.; nonprotein nitrogen, 32 mg.; cholesterol, 205 mg.; and cholesterol esters, 163 mg. per hundred cubic centimeters. The serum albumin level was 4.6 per cent and the serum globulin level 1.4 per cent. The sedimentation rate was 4 mm. during the first hour.

The blood was studied by Dr. Carroll L. Birch. The examination on October 24 showed "hemoglobin

135 Gm per hundred cubic centimeters, 4,600,000 erythrocytes and 31,500 leukocytes per cubic millimeter. The red cells appeared normal in size, and there were no nucleated forms and no polychromia. The platelets appeared normal and were abundant in number

pable, and no enlargement of peripheral lymph nodes was demonstrated. In other words, there was no sign of leukemia except the high leukocyte count and the atypical lymphocytic cells in the peripheral blood. Sternal puncture showed no hyperplasia. The few



Fig 1—Appearance of the face on Oct 21, 1943 A, right side, B, left side

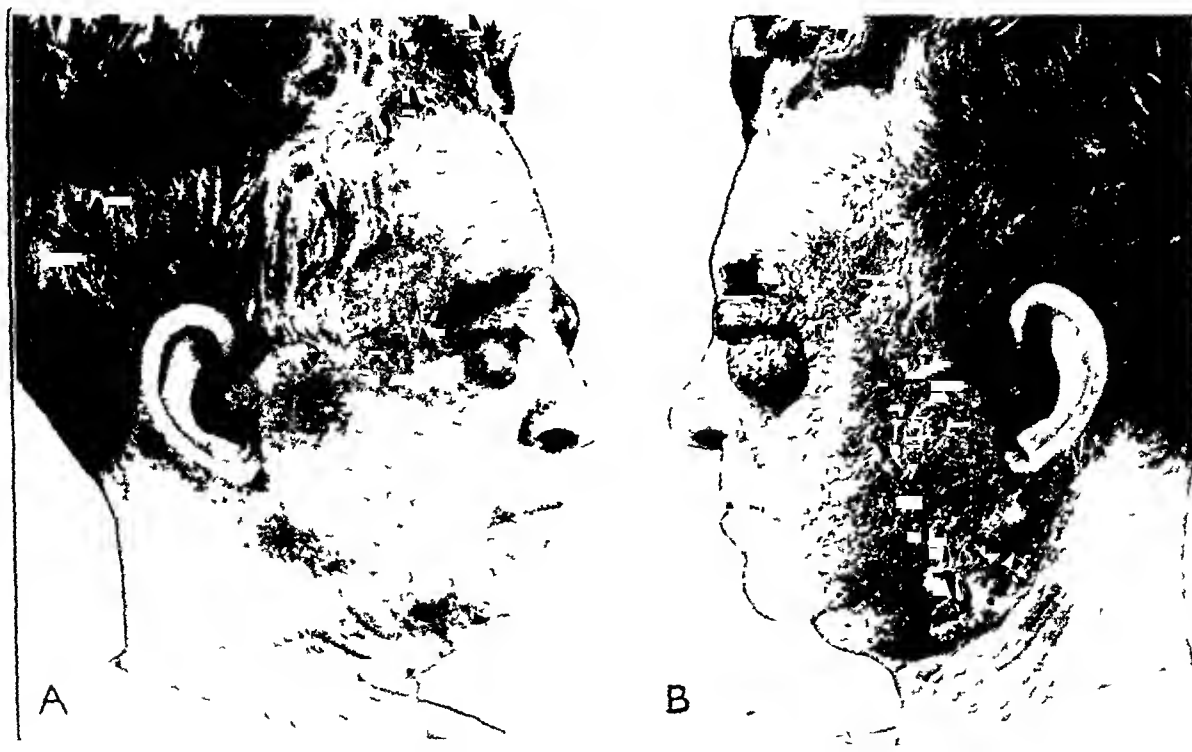


Fig 2—Appearance of the face on Dec 20, 1943 A, right side, B, left side

(390,000). The differential count showed 34 per cent neutrophils, all mature (no shift to the left), although there was an absolute increase in neutrophils. Lymphoid cells were 60 per cent, some of which were young (about 8 per cent showing nucleoli). The remaining 6 per cent were monocytes. The spleen was not pal-

atable, and no enlargement of peripheral lymph nodes was demonstrated. In other words, there was no sign of leukemia except the high leukocyte count and the atypical lymphocytic cells in the peripheral blood. Sternal puncture showed no hyperplasia. The few

Beginning on November 20 the patient was given roentgen ray therapy to the left side of the face, including the left orbital region. Daily exposures of

200 r were given to a field 6 inches (15 cm) in diameter. A total of 3,600 r was administered, using 160 kilovolts, 20 milliamperes and a half value layer equal to 0.6 mm of copper. On Jan 14, 1944 treatment of the right orbital region was begun. A field 5 inches (12.7 cm) in diameter was exposed daily to roentgen rays in doses of 200 r. The factors were the same as those used in treating the left side of the face. A total of 1,200 r was given. Bleeding from the tumor occurred frequently after roentgen ray therapy was instituted. At first there was oozing of small amounts of blood from the left lower eyelid, but occasionally there would be a considerable hemorrhage. Later, bleeding also became frequent from the right eyelids.

The patient was examined finally at home on February 24, after leaving the hospital. By this time he had become emaciated and nearly moribund. The tumor had extended to cover almost the entire head and neck. The entire scalp showed a diffuse dark brown pigmentation, which covered also the back of the neck. On the forehead the skin was smooth and brown. The right eye was open, and the eyelids were purplish brown and wrinkled. The lower right eyelid was partly covered by a bloody crust, resulting from a recent hemorrhage. The lids of the left eye were still swollen shut, but they were covered with bloody crusts and were not as tense as previously. Both cheeks showed a cobble-stone-like surface composed of

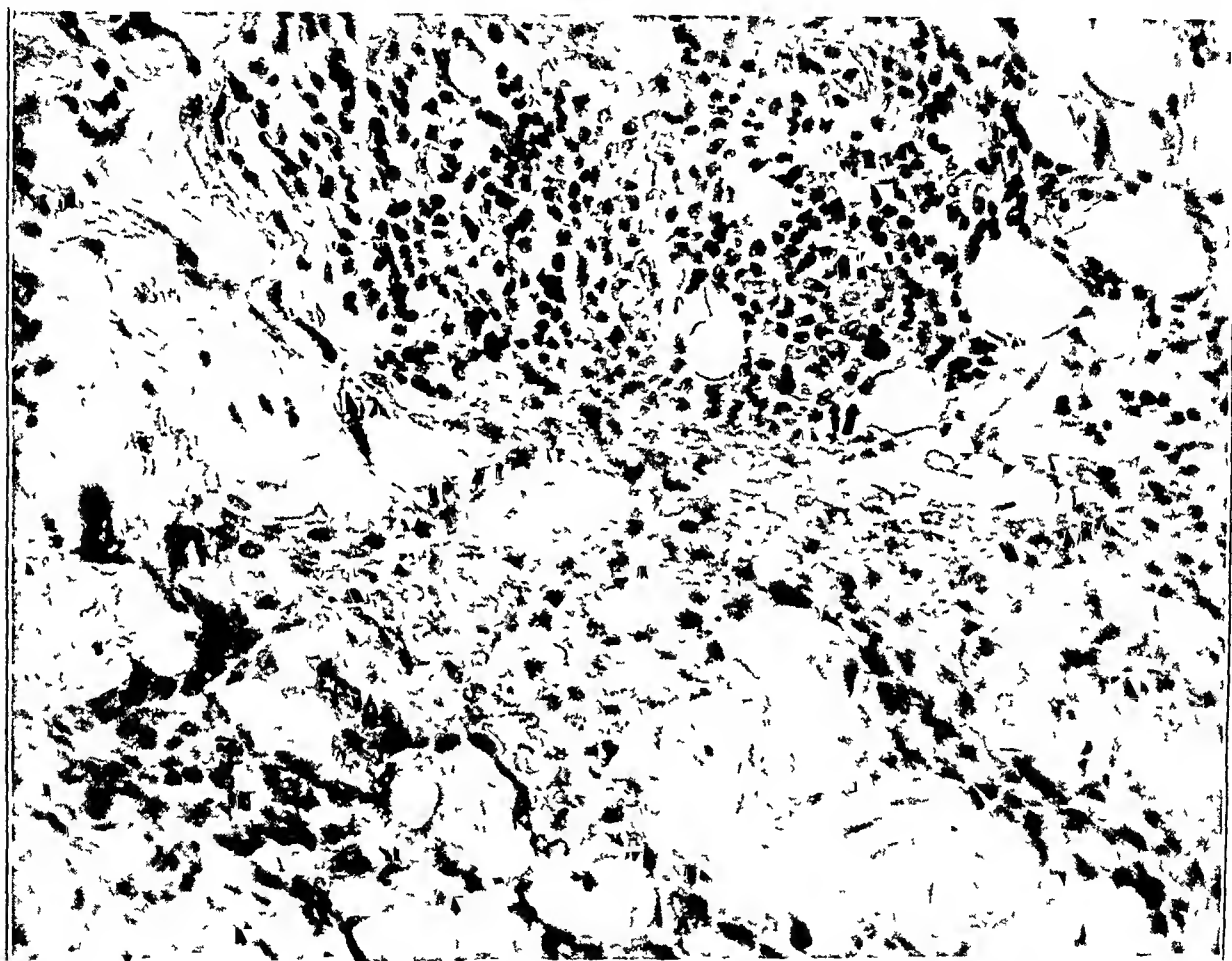


Fig 3—Deeper part of the corium, showing irregularly outlined mass of endothelial cells with many narrow strands of endothelial cells extending from it in all directions. Above lies a nest of atypical lymphoid cells ( $\times 380$ )

and from the tumor on the left side of the jaw. About one month after our first examination a small palpable lymph node appeared on each side below the angle of the jaw. These nodes gradually became larger, but they were never tender or fixed to the surrounding tissues. During the course of roentgen therapy the skin on the forehead became flatter and darker, but the tumor mass continued to extend progressively downward over the sides of the face and neck (fig 2). By this time blood oozed continuously from the left eye. The erythrocyte count dropped to 3,830,000. On January 26 a lymph node on the right side of the neck was removed for histologic study. There was considerable bleeding from the wound, necessitating a transfusion of 500 cc of whole blood.

purplish vascular papules. There was a large exfoliating hemorrhagic crust below the left ear. A large mulberry-like, bluish, soft tumefaction covered the left angle of the jaw, the preauricular area and the tragus of the left ear. The skin on the nose was smooth and reddish brown. The skin on the right side of the face was flattened and slightly wrinkled, and there was less puffing below the right ear than was seen previously. The discoloration involved the entire neck and ended in an indistinct horizontal line at about the level of the larynx. The only parts of the head apparently free from involvement were the middle of the upper lip and the center of the chin. There were several firm, freely movable, nontender nodes in the neck. There were no other lymph nodes palpable. Exami-



nation of the entire cutaneous surface failed to show any lesions that might suggest metastases of the tumor to the skin. The spleen could not be palpated, and there were no changes demonstrable in the border of the liver. The patient died on Feb 28, 1944. Necropsy could not be performed.

*Histologic Examination*—A specimen for biopsy was taken from the skin of the left temple. The surface of the specimen was corrugated, the depressions corresponding to the follicles present, while the elevated portions covered the vascular spaces in the corium. There was a thin non-nucleated scale, and the epidermis was normal except in those areas where it was flattened by pressure of the tumor below. Where the papillae were intact, they contained apparently normal capillaries

ing cords between the fibers of the connective tissue. These cords at first were solid and were composed of several layers of cells. Farther along their course, however, they became canalized to produce narrow vessels lined by one or more layers of endothelial cells (fig 4). In some of these vessels erythrocytes were present, in others atypical lymphoid cells seemed to be taking their origin from the vessel walls. The vessels branched and intercommunicated in all directions to produce a complex and all-pervading network which invaded even the subcutaneous fat and the sweat glands. Adjoining the endothelial masses and about many of the vessels there were many densely packed nests of deeply stained lymphoid cells, which showed variations in the size and staining of their nuclei.

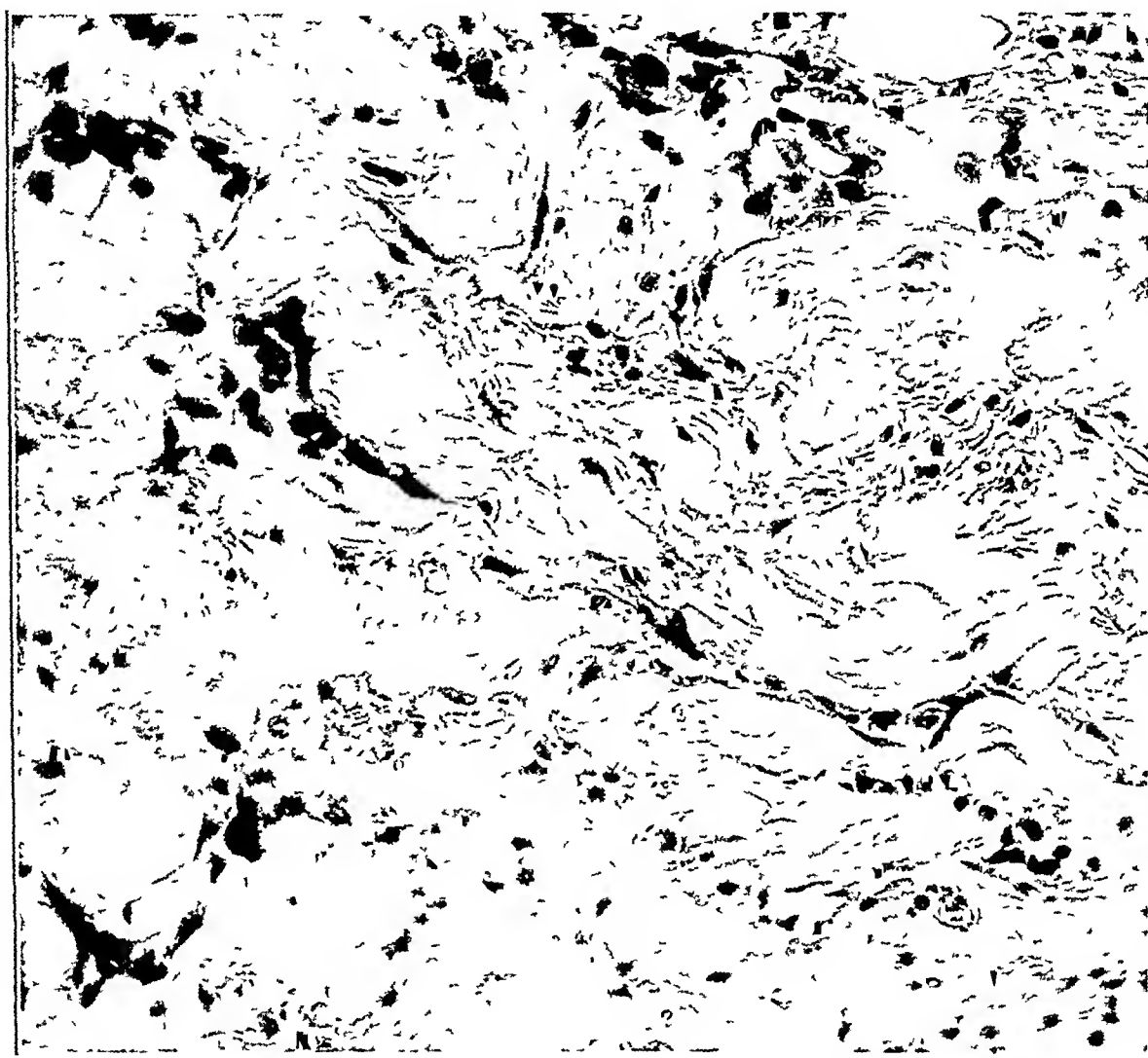


Fig 4—Deeper part of the corium, showing invading cords of endothelial cells which become canalized to produce narrow vessels ( $\times 380$ )

which did not seem to take part in the neoplasia. There were two hair follicles in the section. These seemed normal, and they were surrounded by a narrow zone of dense fibrous connective tissue. Elsewhere the entire corium was permeated by pathologic changes that included masses of cellular infiltrate, strands of endothelial cells, narrow blood vessels and large sinuses.

Deep in the corium there were many irregularly outlined but distinct masses of endothelial cells, giving the impression of a syncytium (fig 3). In some of the cells small vacuoles were seen, and in places these vacuoles coalesced to produce a larger lumen. From these endothelial masses many narrow strands of endothelial cells extended in all directions to lie as invad-

Higher in the corium and extending into the sub-papillary layer the vessels became widened to produce a maze of intercommunicating sinuses (fig 5). In general, these were lined by a single layer of endothelial cells, but in places there was proliferation to several layers. There were many projecting ingrowths from the walls of the sinuses, which tended to fill the lumen and to produce a spongelike appearance (fig 6). These larger ingrowths and many small knoblike projections were composed of a pale-staining fibrous stroma and a covering of a single layer of endothelial cells. The lumen contained, in addition, a few erythrocytes and many monocytes and lymphoid cells, some with nucleoli. These atypical cells had the same appearance as those seen in the peripheral blood and



they doubtless were taking their origin within the tumor. The connective tissue stroma contained many small blood vessels and also a diffuse infiltrate of histiocytes, lymphocytes and connective tissue cells. There were many small brown granules throughout the specimen.

Perles' prussian blue reaction showed iron pigment to be present profusely throughout the specimen. Much of it lay in granules within the histiocytes that were present everywhere in the connective tissue, even in the stroma of the small knoblike projections in the sinuses. The endothelial cells lining the vessels and sinuses, those in the syncytial endothelial masses and the atypical lymphoid cells, however, did not seem to have taken up any granules that were stained by this method. Weigert's stain showed elastic fibers to be

present in the connective tissue stroma. Vascular tumors of the skin are exceedingly rare. The number of cases reported in recent years suggests that a large proportion of these malignant tumors belong to the group of hemangioendotheliomas. One cannot make a diagnosis of hemangioendothelioma on clinical grounds alone, for the tumor may vary in appearance from a small pedunculated nodule to the large invasive mass that was present in our patient. In general, however, these tumors are soft, dark red and raised above the surface of the skin, and they grow slowly but progressively. Pigmentation is often present because of the ten-



Fig 5—Upper part of the corium, showing large sinuses and intercommunicating vessels ( $\times 95$ )

present only as short and narrow strands about the hair follicles, between the tumor cords and about the blood vessels in the matrix. Bielschowsky's silver reticulin stain showed a delicate fibrous mantle about each vessel.

Histologic examination of a right supraclavicular node showed considerable invasion and replacement by large densely packed masses of endothelial cells and by tortuous vessels which were lined by a single layer of endothelial cells (fig 7). Mitotic figures were not seen. Perles' prussian blue reaction showed a small amount of iron pigment within the invaded areas.

#### DIAGNOSIS

Considering the frequency with which one encounters tumors of the blood vessels, malig-

nant vascular tumors of the skin are exceedingly rare. The number of cases reported in recent years suggests that a large proportion of these malignant tumors belong to the group of hemangioendotheliomas. One cannot make a diagnosis of hemangioendothelioma on clinical grounds alone, for the tumor may vary in appearance from a small pedunculated nodule to the large invasive mass that was present in our patient. In general, however, these tumors are soft, dark red and raised above the surface of the skin, and they grow slowly but progressively. Pigmentation is often present because of the ten-

dency for bleeding within the tumor. The response to roentgen ray or radium therapy is generally poor. There is a tendency for recurrence after excision, and metastases when they occur are late in the course of the disease.

The diagnosis may be made most conclusively on histologic examination. The tumor is composed of masses of atypical endothelial cells and vascular tubes which in places are lined by several layers of endothelial cells and which exhibit a tendency for their lumens to anastomose. Often the cells predominate over the vessels. Ewing<sup>21</sup>

stated that "the endothelial cell in tumors usually retains some of the distinguishing features on which alone the recognition of the nature of the growth may often be based. The form is polyhedral, often pavement in type, and occasionally cylindrical. Under pressure it assumes a spindle form, and in edematous tissues it swells to spheroidal form and considerable dimensions. A well-defined cell membrane, relatively clear cytoplasm, small pale vesicular nucleus with minute multiple nucleoli are features so fre-

vessels, as shown by Kettle and Ross<sup>12</sup>. The use of a silver reticulin stain helps to demonstrate the vascular composition of the tumor by impregnating the delicate fibrous framework about each vessel.

Hemangioendothelioma must be differentiated chiefly from hemangioma, granuloma pyogenicum, malignant endothelioma and idiopathic multiple hemorrhagic sarcoma of Kaposi.

Hemangioma generally appears early in life, it is sharply outlined and has a uniformly red

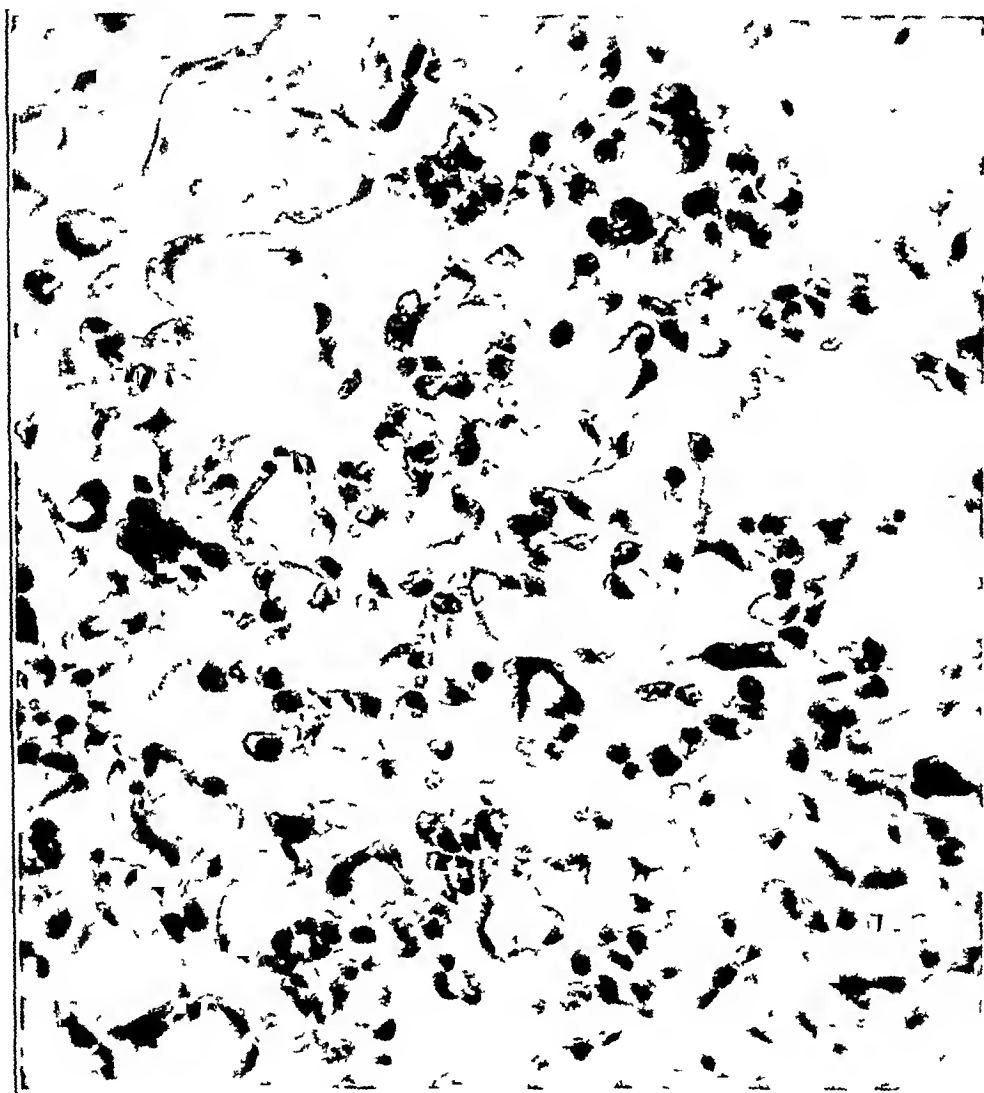


Fig 6—Upper part of the corium, showing intercommunicating young vessels containing atypical lymphoid cells and monocytes ( $\times 380$ )

quently exhibited as to render them valuable diagnostic aids." The endothelial cells often form a syncytium-like mass, and linear strands of these cells extend as invading cords between the fibers of the connective tissue. These cords become canalized to produce vessels which contain blood cells. Often one may also demonstrate the formation of a lumen within the endothelial masses by the development of small intracellular vacuoles which eventually flow together to form at first irregular spaces and eventually elongated

color, and it shows no tendency to bleed or to produce pigmentation. Histologically it is composed of dilated capillaries that are filled with blood and are generally lined by a single layer of normal endothelial cells.

Granuloma pyogenicum frequently appears at the site of an injury, grows rapidly to produce a tumor that is pedunculated or sessile, and bleeds readily to develop a crusted surface or one

<sup>12</sup> Kettle, E. H., and Ross, J. M. A Contribution to the Study of the Endotheliomata, *Lancet* 1:1012, 1921.

covered by a purulent exudate. Histologically there is considerable proliferation of young blood vessels, which are lined by a single layer of endothelium. Often there is a diffuse infiltrate throughout the stroma containing many polymorphonuclear leukocytes, but in some cases there is sufficient proliferation of fibroblasts to make the differentiation from hemangioendothelioma difficult.

Malignant endothelioma cannot always be readily differentiated clinically or histologically from hemangioendothelioma. In the former,

the disease in most cases is prolonged. Histologically there are seen vascular dilatation and small hemorrhages with the deposition of hemosiderin, an infiltrate of lymphocytoid cells and a proliferation of capillaries, an increase in the blood vessels to suggest the appearance of a hemangioma and, finally, the histologic changes suggesting a fibrosarcoma. In many cases all stages of this development may be seen histologically in the same specimen.

In 1921 Highman<sup>13</sup> stated regarding the general problem of diagnosis of tumors that

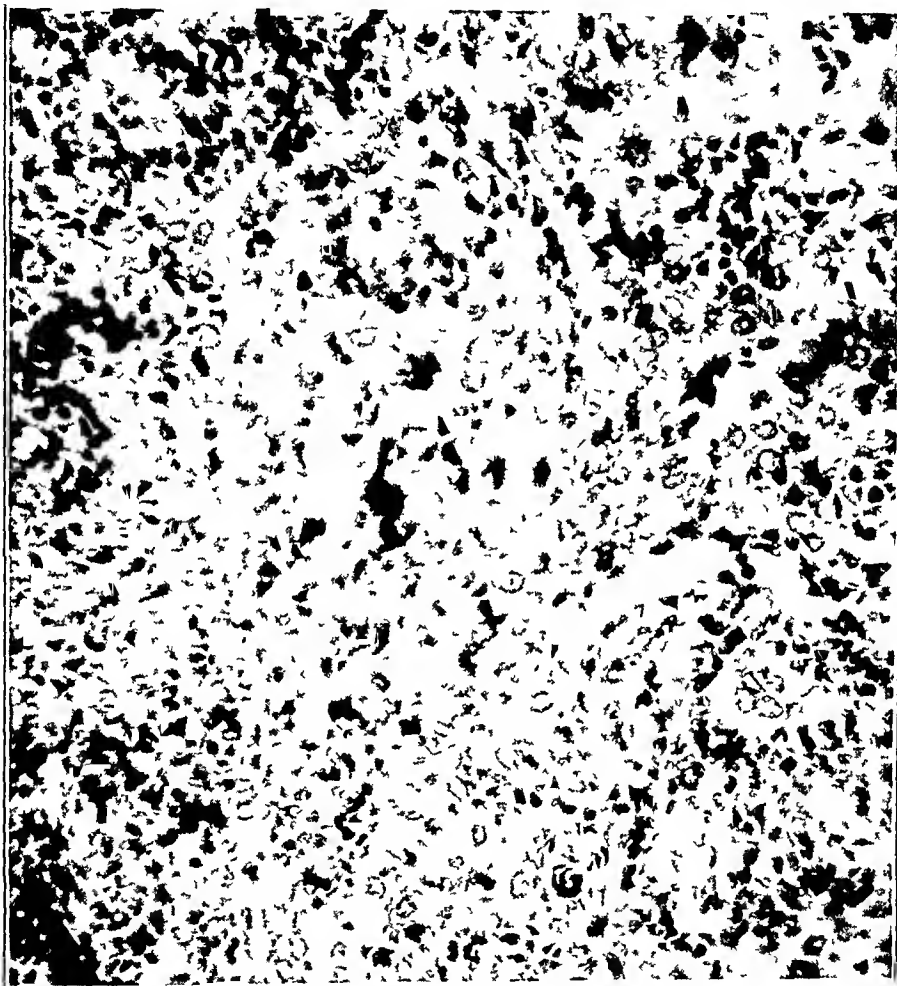


Fig 7—Section from a right supraclavicular node, showing invasion by densely packed masses of endothelial cells and blood vessels ( $\times 300$ )

however, there is a great predominance of cellular elements, there is but little tendency for the development of vessels and mitotic figures are more frequent.

In Kaposi's sarcoma the lesions generally begin as bluish red stains in which a definite infiltration soon develops. The hands and feet are the areas most often involved at first, but any area of the skin may be affected. The lesions enlarge slowly to produce deep, firm nodules, and these may spread gradually to involve large areas. Metastases may appear late, and the course of

"to attempt a diagnosis on clinical grounds alone is often futile and when a diagnosis can be reached only by microscopic study the latter ceases to be an avocation and becomes a duty. Accurate tumor diagnosis is possible only by means of histological investigation." These remarks are still valid as formulating the minimum requirement for establishing the diagnosis of any tumor. In the special problem of tumors of the blood vessels, however, one must correlate

13 Highman, W. J. *Dermatology*, New York, The Macmillan Company, 1921, p. 344.

the histologic changes with the clinical course before one is able to grade these tumors precisely as to diagnosis and prognosis

## COMMENT

The influence of trauma in the production of tumors of the blood vessels is well established. In our patient the tumor appeared soon after injury and at the site of trauma. While we have no proof that there was no lesion present at that site prior to the injury, it is hardly likely that a previous lesion on the scalp would have gone unnoticed in a man of his age. It is interesting to note that, while the growth of the tumor was very slow for about seven months, as it invaded new territory it seemed to become progressively more malignant and more proliferative. Hueper<sup>14</sup> listed a number of cases in which a hemangioma appeared at the site of trauma. Ewing<sup>15</sup> stated that "in the etiology of endothelioma, the influence of chronic irritation or trauma and low grades of inflammation must be given a prominent place." Busman<sup>16</sup> reported 3 cases of malignant endothelioma, in 2 of them preceded by trauma and in 1 by a boil. Trauma was a factor in cases reported by Downing and Mallory,<sup>6</sup> Markowitz,<sup>7</sup> Sweitzer and Winer<sup>10</sup> and Stout<sup>4</sup> (cases 8 and 14).

The leukemoid blood picture was sufficiently striking to make it seem at first that we were dealing with true leukemia. The presence of cells originating from the endothelial walls of the tumor vessels, identical with the atypical lymphoid cells in the circulating blood, makes it plausible to assume, however, that the high leukocyte count was the result of the overproduction of these cells within the tumor. While treatment with roentgen rays had little effect on the growth of the tumor, it seemed to cause a temporary diminution in the production of these atypical cells. Soon after the treatment was instituted on November 20, the blood count showed a drop to 30,200 leukocytes on November 24 and to 12,700 on Dec 2, 1943. Thereafter there was a gradual rise in spite of continued roentgen ray treatment, and the count on December 15 showed 13,750 leukocytes on January 7 18,400 and 21,100 on Jan 27, 1944.

14 Hueper W C. Occupational Tumors and Allied Diseases, Springfield, Ill., Charles C Thomas, Publisher, 1942, p 654

15 Ewing,<sup>3</sup> p 348

16 Busman, G J. Malignant Endotheliomas with Cutaneous Involvement, Arch Dermat & Syph 6 680, 1922

Orzechowski<sup>17</sup> described a malignant hemangioendothelioma of the liver in a 2½ month old girl, in which early forms of blood cells were found inside the newly formed capillaries of the tumor and its metastases. This case and the one reported by us suggest that in hemangioendotheliomas primitive mesenchymal tissue may be the ancestor of both the vasoformative cells and the cells seen in the circulating blood.

## SUMMARY AND CONCLUSIONS

A case of hemangioendothelioma of the skin in a 75 year old man was observed. The tumor was a bluish red, pigmented, infiltrative mass which appeared on the scalp at the site of trauma, spread slowly over the face, scalp and neck, produced late metastases to the cervical lymph nodes and resulted in death nineteen months later. Leukocytosis was present, and large numbers of atypical leukemoid cells were found in the peripheral blood and in the sinuses of the tumor. Treatment with roentgen rays had but little effect on the growth of the tumor.

Malignant vascular tumors are rare. A review of the literature suggests that a large proportion of such malignant tumors belongs to the group of hemangioendotheliomas. Trauma appears to be an important factor in the causation of many of them. A diagnosis of hemangioendothelioma cannot be made on clinical grounds alone but depends on the demonstration of typical histologic changes. The tumor is composed of masses of atypical endothelial cells and vascular tubes which in places are lined by several layers of endothelial cells and which exhibit a tendency for their lumens to anastomose.

Hemangioendothelioma must be differentiated chiefly from hemangioma, granuloma pyogenicum, malignant endothelioma and idiopathic multiple hemorrhagic sarcoma of Kaposi.

## ABSTRACT OF DISCUSSION

DR SAMUEL E SWEITZER, Minneapolis. I wish to congratulate Dr Caro for his interesting paper before this association.

My interest was stimulated a few years ago by the paper Dr Winer and I wrote. I think that we had 6 cases, and the feature that struck us in making the diagnosis was the appearance of ropes of endothelial cells that infiltrated into the surrounding tissue in this disease. That was quite distinctive in our findings and apparently was found in this case. I think one could—in fact, we did in some of ours at least—excise them. Hemangioendothelioma has a relatively low degree of malignancy. When it occurs, especially in places where it can be excised, excision is the best treatment.

17 Orzechowski, G. Ueber die primären blutbildenden Hämangioendotheliome der Leber, Virchows Arch f path Anat 267.63, 1928

DR JOHN G. DOWNING, Boston I wish to congratulate Dr Caro on his paper. I have had 3 patients with hemangioma alleged to have resulted after trauma. The first was the one mentioned in this paper. This patient is still alive. At first it was thought that surgical intervention would be of no value, but it was tried when it was observed that the patient's left eye was beginning to close because of the extensive growth on the upper lid. A successful operation was performed at this area, but later there was definite extension of the disease and further surgical measures were advised against. The next patient was a man who lost his leg in an automobile accident. On the great toe remaining there was a bluish violet growth which was removed surgically. Shortly afterward new lesions appeared on the inner aspect of that thigh. The last was a court case. The history stated that the man was struck on the back by a ladder. The testimony of the general practitioner supported the contention that he had ecchymosis at this area, and later a purplish violaceous lesion developed at that site. The man died, and at autopsy an extensive endothelioma-hemangioma of the liver was disclosed. Incidentally, the hemangioma was not discovered until the man entered the hospital for treatment of his liver. New growths appearing after trauma should have definite satisfactory proof. Perhaps after this war more lesions of this type will be seen, as a result of the explosive forces to which military personnel are exposed.

DR MARCUS R. CARO, Chicago I wish to thank Dr Sweitzer and Dr Downing for their discussion. I am sorry that Dr Montgomery was unable to remain to discuss this paper, for he examined sections and concurred in the diagnosis of hemangioendothelioma. Both he and Dr Broders classified the tumor histologically as a grade 1 hemangioendothelioma.

I believe that the clinical course of this patient, with the progressive extension of the tumor in spite of intensive treatment and with eventual metastasis to the lymph nodes, gave the prognosis much more accurately than it could have been established histologically. One

cannot always tell from an examination of a section of a tumor just what is going to happen to the tumor in the future.

Dr Montgomery, in a personal communication, also stated that he was a little hesitant about acceptance of the group of malignant endotheliomas, feeling that such tumors are usually hemangioendotheliomas or hemangiosarcomas. I think that there is less and less tendency to classify tumors as hemangiosarcomas. In designating malignant vascular tumors as angiosarcomas, one would at times include vascular tumors of various origins, for sarcomas of all types are often vascular. The growth of sarcomas is generally accompanied by a proliferation of the preexisting blood vessels of the invaded tissue. Because the vascularity of many of these tumors is a vascularity of the stroma rather than of the tumor itself, the term angiosarcoma is being applied less and less often while many vascular tumors are being identified more properly as chorioepitheliomas, hypernephroid carcinomas, etc. For tumors in which the proliferating cell is the endothelial cell, the term hemangioendothelioma or malignant endothelioma is preferable, the choice depending on the predominance of cells over vessels and the number of mitotic figures present.

In answer to Dr Downing's remarks, I think that trauma is often an etiologic factor in such cases. In granulation tissue new vessels develop by the sprouting of endothelial cells from preexisting capillaries to form solid cords which then become canalized to produce vessels. It is possible that in cases such as the one we are reporting and others associated with trauma the injury results in an identical production of new blood vessels, which in their further growth become infiltrative and eventually malignant. A number of cases in the literature report an injury to a site where there was no preexisting lesion, followed by the development of vascular tumors which eventually caused death. Hueper, in his excellent book on "Occupational Tumors and Allied Diseases," cited a number of reports of vascular tumors following trauma.



# EXFOLIATIVE DERMATITIS DUE TO SULFATHIAZOLE

## REPORT OF A CASE CHARACTERIZED BY RECURRENT ATTACKS WITH BEAU'S LINES AND ALOPECIA

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Exfoliative dermatitis due to the administration of sulfonamide drugs is relatively rare. A case with fatal termination following the use of sulfathiazole was reported by Weinstein and Domm (1941).<sup>1</sup> Their case merits note in that the patient had a history of a severe cutaneous rash twelve years before, following arsenotherapy for syphilis. Johnson (1944)<sup>2</sup> described a case of severe exfoliative dermatitis, with recovery, caused by sulfadiazine. The case to be described is of interest for the following reasons: 1. Sensitization apparently resulted from the previous ingestion of only 3 Gm of sulfathiazole. 2. A repetition of the attack of exfoliative dermatitis was produced by the ingestion of only 1 Gm of sulfathiazole. 3. Transverse furrows of the nails (Beau's lines) together with alopecia accompanied each attack of dermatitis.

### REPORT OF CASE

F. P., first seen on June 20, 1944, was a highly intelligent Negro man, aged 23. He complained of desquamation and itching of his skin, abnormal nail formation and loss of hair. He was not acutely ill.

On March 13, 1944 he noted an itching vesicular eruption of his face. In the course of a few days the eruption spread over the entire face, with the formation of rough, oozing, yellow crusts. There were no lesions on the body or extremities. He was hospitalized with a diagnosis of impetigo and treated with wet dressings and a sulfur ointment. After a week of this treatment the lesions cleared. Systemic symptoms were not present at any time.

Administration of sulfathiazole, 15 Gm three times daily, was begun on April 7, 1944, in the belief that it would "improve his skin and prevent a recurrence." No lesions were present at this time. On April 9 he noted severe itching, and on the following day his skin "peeled off with his shirt." Subsequently, severe generalized desquamation, oozing and fissuring, with great attendant discomfort, developed. In a few days his vision became very poor, in part as a result of exces-

sive lacrimation and blepharitis, and he was unable to recognize faces at more than 5 feet (1.5 meters). A foul aural discharge with frequent blocking of the meatuses, blocking of the nostrils with bloody crusts, whitish desquamation of the scalp with diffuse loss of hair and denudation of the palms and soles leaving a raw, painful surface followed. Continual chilly sensations with frequent shivering were experienced.

The administration of sulfathiazole was stopped on April 12. On April 16 moderate edema of the ankles with bilateral inguinal adenopathy appeared. The adenopathy was painless and reached a maximal diameter of 2 inches (5 cm) in four days. There was no history of a genital lesion other than those associated with the generalized exfoliation.

A simple ointment was applied to the skin. One month later the skin was nearly normal. Edema of the ankles and inguinal adenopathy persisted. The nails of fingers and toes had become thickened and rough at the base and presented a transverse furrow. The patient felt well, and his vision had returned to normal. Because of the persistent adenopathy and edema of the ankles, he was again given sulfathiazole. Four and one-half hours after he had taken 1 Gm of the drug his temperature was 104 F. Severe itching ensued and was followed in three days by a repetition of the generalized exfoliation previously described. Five weeks of treatment with simple ointments improved him sufficiently to permit his release from the hospital. At this time he noted a second transverse furrow on the nails.

The past history of the patient failed to reveal any previous dermatitis or serious illness. In February 1943 he began to have difficulty in breathing through the nares, which became progressively worse. Surgical removal of multiple nasal polypi in December 1943 relieved this complaint. No oral medication was given at this time. He never suffered from eczema, migraine or asthma. On Feb 10, 11 and 12, 1944 he had taken a total of 3 Gm of sulfathiazole, on the advice of a friend, for a slight pain in his chest. No medication had ever been received parenterally.

*Physical Examination*—The patient was a well developed and well nourished man. No abnormalities were found on examination of the various systems.

The skin was dry, with easily detached fine white scales. The skin of the extremities was noticeably thickened, especially in the cubital and popliteal fossae, where the normal flexure markings were greatly accentuated. Sweating was minimal. A partial alopecia involved the vertex and occiput, the hair of the temporal regions having grown back fairly well. The hair was lanugo-like in the areas of regrowth. The nails of the fingers and toes were thickened and dystrophic and had a pair of transverse furrows on each nail.

1 Weinstein, M., and Domm, A. H. Development of Acute Exfoliative Dermatitis During Administration of Sulfathiazole, I. A. M. A 117:607-608 (Aug 23) 1941.

2 Johnson, R. D. Generalized Exfoliative Dermatitis Due to Sulfadiazine. I. A. M. A 124:979-980 (April 1) 1944.



continue with a gainful pursuit provided adequate rest and definite periodic vacations are enforced. A well balanced nutritious diet containing an excess of red meat, liver and vitamin C furnishes an accessory defense for the blood vessels and their passengers. The use of arsenic for patients with this disease is not advised because of its fundamental property of stimulation of epithelial and cellular tissue and its related toxic effects, including late epitheliomatous changes.

The manner in which the roentgen rays are employed is of the utmost importance. In the stages of dermatitis and superficial infiltration, the lesions will respond to therapy of low voltage unfiltered rays. The formula advised is as follows: 60 to 100 kilovolts, 3 to 5 milliamperes, 15 to 20 cm focal skin distance, and inherent filtration of the tube. The approximate half value layer for this formula is 1 to 1.5 mm of aluminum. The dosage (free air exposure measured at the surface of the skin) varies from 75 to 200 r per area weekly. The individual lesions respond to a total dose of 600 to 800 r. The areas treated are screened off to include a border of normal skin of approximately 0.5 to 2 cm. It must be remembered that the amount of back scatter varies with the half value layer and attains a maximum at a half value layer of about 0.4 to 0.6 mm of copper. This value is usually obtained with a kilovoltage of 150 and a filtration equivalent to 2 to 4 mm of aluminum or 0.25 mm of copper. When the voltage is increased above this value, the back scatter is decreased. This would, of course, lower the skin dose for a given air dose. Areas such as the thyroid, testes and hairy regions should be properly shielded.

This therapeutic regimen is radically altered if the lesions are considerably infiltrated or are of the tumor variety (including the d'emblee type). In view of the desirability of employing rays of greater penetration (harder, higher frequency, shorter wavelength) the formula is correspondingly modified. The factors now range from 120 to 150 kilovolts, 5 to 10 milliamperes, 15 to 25 cm focal skin distance, and filtration of 2 mm of aluminum to 0.25 mm of copper. The free air exposure measured at the skin surface should be increased to 200 to 400 r per area at five day intervals for a total dosage of 1,000 to 1,600 r. Occasionally it is observed that a single exposure of 400 r will literally melt away elevated and infiltrated lesions. However, this is not of usual occurrence. The

areas undergoing treatment should be screened off to include 2 cm of normal tissue. If the lesions overlie important and radiosensitive tissues, such as the ovaries, salivary glands, and testicles, in addition to careful shielding, the beam of radiation should be directed obliquely to avoid injury to these tissues. Occasionally this may necessitate cross fire radiation of the involved site. In treating large areas, it should be recalled that back scatter is at a maximum with radiation of this quality. This additional radiation may be considerable (for example, with the formula just described it is approximately 25 per cent of the primary beam for a 25 sq cm field). When a wide range of fields and of qualities of radiation are employed, it is essential to employ the skin dose rather than the air dose. As is known, the skin dose is the sum of the primary beam and the back scatter. The latter may be easily computed with the aid of available tables. The question of expressing dosage in terms of roentgens or of erythema units depends on the individual therapist. The number of roentgens necessary to produce an erythema varies considerably with the quality of the radiation. It may be determined experimentally with the particular x-ray machine employed.

In some patients with extensive involvement radioresistance may occur. For them it may be of value to institute a short series of fever therapy treatments before attempting larger doses of roentgen rays. The essential mechanism of these hyperpyrexial treatments is not known but may be assumed to lead to various biochemical and immunologic changes which render the tissues more responsive to roentgen rays.

#### SUMMARY

A case of mycosis fungoides is described in order to illustrate the value of controlled radiotherapy in this disease. The patient received 67,000 roentgen units with no discernible toxic effects. The general care and management of this disease is discussed. The technical and detailed aspects of proper administration of roentgen ray therapy in this disease are enumerated. Contrary to the general conception of therapy in mycosis fungoides we are opposed to the administration of arsenic for this disease for reasons mentioned in the preceding comment. It is to be emphasized that with proper therapy the life span of patients with mycosis fungoides may be appreciably lengthened.

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# SOME PHASES OF VITAMIN THERAPY IN DERMATOLOGY

MAXIMILIAN E OBERMAYER, M D

AND

KENDAL FROST, M D

LOS ANGELES

Vitamin therapy in the dermatologic field is used for a variety of diseases, which may be divided into two groups (1) the true and established vitamin deficiencies and (2) dermatoses in which a true vitamin deficiency is either debatable or undemonstrable but for which vitamin therapy appears to be of benefit. Some dermatoses of the latter group are the subject of our discussion.

Vitamin therapy in dermatology presents certain peculiarities which must be appreciated if satisfactory results are to be achieved. For most diseases which yield to treatment with vitamins infinitely higher doses are required than are provided by dietary measures or by the administration of commercially advertised vitamin concentrate mixtures. Moreover, the route of administration plays at times an important, if yet unexplained, role (Spies and Butt<sup>1</sup>). In selecting vitamin products one has the choice of synthetic vitamins and the natural concentrates. The pure crystallized chemical compounds would be preferable because the vehicle for the natural concentrates may be the source of allergic reactions. However, there are indications that, as in the case of estrogenic substances, the effect of the two types may not be identical (Stokes).

The following discussion of the effect of vitamin therapy on a number of diseases of dermatologic interest is based on our own experience as well as on the published reports of other observers.

## THE ALLERGIC STATE

An important and as yet not generally recognized effect of a high intake of vitamins A, C and D and the B complex is its aid in the control of the allergic state. In certain chronic recurrent inflammatory dermatoses, for instance the dry form of neurodermatitis (atopic dermatitis) and some forms of chronic urticaria it is well established that the accompanying phe-

nomena of dermal hypersensitivity, indicated by positive reactions to dermal tests, vary in intensity from time to time in the same patient. It has further been established that the threshold of allergic response may be raised or lowered at a given time by the state of emotional tension and by other factors. As has been pointed out by one of us (M E O<sup>2</sup>), there are a large number of cutaneous diseases in which the allergic factor is only one link in a chain comprising several causal elements, of which the functional, the bacterial and the toxic are others, hence any therapy which aids in the control of that allergic link is a welcome addition to the management of these dermatoses. How this effect is accomplished by vitamin therapy is not clear. Stokes has expressed the opinion that it may be due in part to the action of the vitamin B complex on the intestinal tract and perhaps to the anti-dermatitis and hypochlorhydria-preventing fractions. In this connection it is interesting that the heterogeneous group of chronic inflammatory dermatoses which Gross<sup>3</sup> reported were beneficially affected by vitamin B complex therapy were characterized by low gastric acidity. It is, then, not improbable that the antichlorhydria fraction of vitamin B complex deserves the credit, for the beneficial effect of the administration of hydrochloric acid to patients with chronic inflammatory dermatoses who have an allergic diathesis appears well established. On the other hand, the importance of the pyridoxine content of the vitamin B complex was stressed by Wright<sup>4</sup>. Whatever the explanation, we can only confirm the beneficial effect of large doses of vitamin B complex in the therapy of this group of dermatoses. It may be administered in the form of injections of crude liver extract.

<sup>2</sup> Obermayer, M E. Functional Factors in Common Dermatoses, *J A M A* **122** 862-864 (July 24) 1943.

<sup>3</sup> Gross, P. Non-Pellagrous Eruptions Due to Deficiency of Vitamin B Complex, *Arch Dermat & Syph* **43**:504-531 (March) 1941.

<sup>4</sup> Wright, C S, Samitz, M H, and Brown, H. Vitamin B<sub>6</sub> (Pyridoxine) in Dermatology, *Arch Dermat & Syph* **47** 651-653 (May) 1943.

From the Department of Dermatology of the University of Southern California.

<sup>1</sup> Dancin G G. Diseases of Metabolism Philadelphia W P Saunders Company 1942 p 448.

two or three times a week, or it may be given by mouth. For patients who require sedation, one of us (M E O) prescribes routinely a mixture of equal parts of elixir of phenobarbital and one of the commercially available liquid vitamin B complex concentrates.

#### DISEASES CHARACTERIZED BY EXCESSIVE KERATINIZATION OF EPITHELIAL TISSUES

Large doses of vitamin A seem to affect a large number of dermatologic diseases by their influence on the integrity and resistance of epidermal and epithelial surfaces. It has been claimed that vitamin A serves as an important buffer against pyogenic infection, but it seems probable that its effect is only indirect and that excessive keratinization of epithelium paves the way for infection. The mechanism of the effect of vitamin A on the epithelial tissues has not been explained. The skin contains no appreciable quantities of the vitamin, and carotenoid levels of the blood plasma of patients with a number of diverse cutaneous diseases have not revealed characteristic deviations (Cornbleet and associates<sup>5</sup>). Vitamin A, because of its solubility in fats, is absorbed through the human skin (Mandelbaum and Schlesinger<sup>6</sup>). In view of the possibility of localized demands for vitamins, it may be that in the treatment of local lesions the applications of vitamin A in anhydrous wool fat is most effective, because of the likelihood of greater local concentration of the vitamin, a question which deserves further study.

The diseases characterized by excessive keratinization of epithelial tissue may be divided into two groups: (1) those in which keratinization is more or less diffuse and (2) those in which the disturbance is limited to the follicular system.

*Group 1 Calluses, Corns, Keratoses.* The value of vitamin A therapy in the treatment of patients with an abnormal tendency to formation of calluses is definite. Successful treatment of corns with this vitamin was reported by Straumfjord<sup>7</sup>. Keratosis blennorrhagica likewise yields to the administration of vitamin A (Combes and Behrman<sup>8</sup>). We wish to call attention to a so

far neglected field for investigation of vitamin A therapy, namely, common inflammatory dermatoses which in themselves would not be considered suitable for such treatment were it not for the fact that some patients have lesions which show an abnormal degree of keratinization and a complete lack of response to orthodox methods of therapy. As an illustration, the following cases from the practice of one of us (M E O) are reported.

**CASE 1**—M M, a 50 year old Caucasian woman, had a highly pruritic, erythematous, thickened and lichenified plaque several centimeters in diameter just below the right knee. The lesion had been present for many years and had been treated by recognized dermatologists in various parts of the country with a host of local applications, including roentgen irradiations to the limit of tolerance, with only transient success. In addition, plaques of dry erythematous dermatitis were present on the eyelids, the neck, the lower part of the back and the extensor surfaces of the arms and legs. The latter were of only short duration, and the patient stated that she had had several attacks of dissemination of the original dermatosis. In view of the clinical appearance of the lesions, the negative results of laboratory examinations and the personality of the patient, a diagnosis of dry neurodermatitis was made, and the plaque on her knee was regarded as an unusually hyperkeratotic type of lichen simplex chronicus. General and local treatment was instituted, with the result that within a few weeks all the lesions disappeared with the exception of the plaque on the knee, which remained refractory to all types of local applications, even occlusive dressings effected only partial improvement of this lesion. However, when she was given 50,000 units of vitamin A three times a day, the plaque disappeared completely in two months, and the skin has remained clear for the last six months.

**CASE 2**—O J, a 30 year old Caucasian woman, had a plaque similar to that of M M (case 1) on the anterior surface of the right instep and ankle. It was so pruritic that she was unable to refrain from scratching, and as a result the surface was at times covered with a sanguineous crust. Two small lichenified plaques were also present just below the elbows. The eruption, which was of five years' duration, had been unsuccessfully treated by several physicians. General and local measures had had no effect on the dermatosis. The patient was of the "high-strung" type and was subject to migraine. As in case 1, a diagnosis of lichen simplex chronicus with unusual hyperkeratinization of the plaque on the leg was made and treatment was instituted. Also as in case 1, the lesions, except for the hyperkeratotic plaque, cleared, but it remained refractory to anything but the application of occlusive dressings, which effected partial improvement. However, when she was given 50,000 units of vitamin A three times daily, the plaque disappeared within three months, and it has not recurred during a five month period of observation.

*Group 2 Asteatosis, Lichen Pilaris, Keratosis Follicularis, Pityriasis Rubra Pilaris, Acne Vulgaris.*—Although the influence of vitamin A therapy on keratotic changes in the follicles is somewhat better understood than its effect on diffuse keratotic changes, because follicular keratinization is one of the outstanding symptoms

5 Cornbleet, T, Popper, H, and Steigmann, F. Blood Vitamin A and Cutaneous Diseases, *Arch Dermat & Syph* 49 103-106 (Feb) 1944

6 Mandelbaum, J, and Schlesinger, L. Absorption of Vitamin A Through Human Skin, *Arch Dermat & Syph* 46 431-442 (Sept) 1942

7 Straumfjord, J V. Lesions of Vitamin A Deficiency, *Northwest Med* 41 229-233 (July) 1942

8 Combes, F C, and Behrman, H T. Use of Vitamin A in Keratosis Blennorrhagica, *Arch Dermat & Syph* 46 728-733 (Nov) 1942

produced by true vitamin A deficiency, the situation is by no means clear. While it is reported that ichthyosis, for example, is not benefited by vitamin A therapy (Peck, Glick and Chargin<sup>9</sup>), asteatosis, lichen pilaris and lichen spinulosus seem to respond to administration of the vitamin (Sulzberger,<sup>10</sup> Lehman and Rapaport<sup>11</sup>). However, it should be remembered that asteatosis and lichen pilaris are not clearcut etiologic entities and that they frequently represent mild degrees of ichthyosis, follicular "id" reactions or even toxic reactions to drugs. It would therefore be unjustified to expect these clinical entities to show a uniform response to vitamin A therapy. Gross<sup>12</sup> has expressed the opinion that the beneficial effect of vitamin A in cases of the ill defined eruption called "nummular eczema" may be explained by the fact that patients with this disease often have dry skins. The beneficial effect of vitamin A therapy on the two rare and obscure follicular dermatoses, keratosis follicularis and pityriasis rubra pilaris, has been definitely established (Peck and associates,<sup>13</sup> Carleton and Steven,<sup>14</sup> Brunsting and Sheard<sup>15</sup>) and represents the only promising mode of treatment of these otherwise intractable dermatoses.

The recent report by Straumfjord<sup>16</sup> has awakened interest in the relations of vitamin A therapy to acne vulgaris. Straumfjord has made the claim that the daily administration of 100,000 U S P units of vitamin A for periods of from nine to eighteen months resulted in the disappearance of the lesions of acne in all but

3 of 100 cases. Such startling results in the treatment of a disease which is admittedly of multiple causation can hardly be accepted without confirmation. We have therefore undertaken the task of repeating Straumfjord's experiments in the treating of patients with acne encountered in a large local institution. The results of this study, which has been under way for several months and will be continued for at least two years, will be reported. At this time we are prepared to state only that vitamin A therapy is undoubtedly of benefit in the handling of some forms of acne vulgaris while others do not seem influenced by it. It seems that acne which is characterized by prominent follicular plugging in addition to the formation of comedos responds most readily to this form of treatment. Such a response appears plausible when it is realized that this pathologic feature is identical with the hyperkeratosis of the pilosebaceous follicle seen in avitaminosis A. It seems significant that in true vitamin A deficiency, as well as in acne vulgaris, the maximal degree of follicular hyperkeratosis is present during adolescence. Frazier and co-workers<sup>17</sup> have shown that the state of sexual development is the critical factor which conditions the response of the pilosebaceous structures to a deficiency of vitamin A. The follicular changes appear in a gradually progressive form as the child grows older, reach their peak during adolescence and diminish in intensity with increasing age.

#### CHEILOSI (PERLÈCHE)

The general contention that cheilosis is always a manifestation of riboflavin deficiency and can be made to disappear by the administration of riboflavin has proved to be erroneous. In some cases perlèche resists vitamin therapy of any type. There is no doubt that this dermatosis may be due to factors unrelated to the vitamins, such as epithelial hypersensitivity to such substances as dyes (in lipsticks) or flavoring matter (in chewing gum). Moreover, it is often forgotten that perlèche as was pointed out by one of us (M E O<sup>18</sup>) is essentially an intertriginous eruption, and it is possible that any factor which increases the apposition of the upper and lower lips can be operative in the production of this condition as well as any other derma-

9 Peck, S M, Glick, A W, and Chargin, L. Vitamin A Studies in Cases of Ichthyosis, *Arch Dermat & Syph* 48 32-34 (July) 1943

10 Sulzberger, M B, in discussion on Brunsting and Sheard<sup>15</sup>

11 Lehman, E, and Rapaport, H G. Cutaneous Manifestations of Vitamin A Deficiency in Children, *J A M A* 114 386-393 (Feb 3) 1940

12 Gross, P. Nummular Eczema. Clinical Picture and Successful Therapy, *Arch Dermat & Syph* 44 1060-1077 (Dec) 1941

13 Peck, S M, Chargin, L, and Sobotka, H. Keratosis Follicularis (Darier's Disease). Vitamin A Deficiency Disease, *Arch Dermat & Syph* 43 223-229 (Feb) 1941. Peck, S M, Glick, A W, Sobotka, H, and Chargin, L. Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease), *ibid* 48 17-31 (July) 1943

14 Carleton, A, and Steven, D. Keratosis Follicularis, *Arch Dermat & Syph* 48 143-150 (Aug) 1943

15 Brunsting, L A, and Sheard, C. Dark Adaptation in Pityriasis Rubra Pilaris, *Arch Dermat & Syph* 43 42-61 (Jan) 1941

16 Straumfjord I V. Vitamin A. Its Effect on Acne. *Northwest Med* 42 219-225 (Aug) 1943

17 Frazier, C N, Hu, C K, and Chu, F T. Variations in Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty, *Arch Dermat & Syph* 48 1-14 (July) 1943

18 Becker, S W, and Obermayer, M E. Modern Dermatology and Syphilology, Philadelphia J B Lippincott Company, 1943

titis intertrigo. In some cases the shape of the mouth is responsible, in others, improperly fitted dentures are the cause of the intertriginous configuration, which through maceration and resulting loss of epithelial resistance leads to an increase of the pyogenic and/or yeast flora and eventual inflammatory reaction. Such anatomic causes and the possibility of epithelial hypersensitivity (eczema) should be ruled out before vitamin therapy is instituted. If neither of these conditions is present and vitamin therapy appears indicated, a trial should first be made with the administration of 5 mg of riboflavin three times daily. If no response is elicited, pyridoxine (vitamin B<sub>6</sub>) should be administered, for it was shown by Machella<sup>19</sup> that cheilosis may yield to the administration of pyridoxine when the ingestion of riboflavin did not affect the disease. On the other hand, it was stated by the same author<sup>20</sup> that patients with cheilosis who failed to respond to treatment with riboflavin and pyridoxine were benefited by the administration of nicotinic acid and that the remainder of the group which responded to none of the three vitamins, was cured by the administration of the entire vitamin B complex in the form of liver extract or brewers' yeast. In view of such observations, it is apparent that the influence of vitamin therapy on cheilosis is by no means clear and requires further systematic study.

19 Machella, T. E., and McDonald, P. R. Studies of the B Vitamins in the Human Subject. Failure of Riboflavin Therapy in Patients with the Accepted Picture of Riboflavin Deficiency, *Am J M Sc* **205** 214-223 (Feb) 1943.

20 Machella, T. E. Studies of the B Vitamins in the Human Subject. The Response of Cheilosis to Vitamin Therapy, *Am J M Sc* **203** 114-120 (Jan) 1942.

#### INSECT BITES

The increasing importance of insect bites as a hazard to health justifies our calling attention to a peculiar effect produced by the internal administration of thiamine hydrochloride. If this effect is confirmed, thiamine hydrochloride may serve as an effective aid in the treatment and prevention of insect bites. Shannon<sup>21</sup> has reported data from a number of cases which seem to indicate that thiamine hydrochloride in adequate doses, administered either by mouth or by injection, is capable of causing previously susceptible persons not only to tolerate but actually to repel the offending insects.

#### SUMMARY

Vitamin A may be beneficial in the treatment of diseases characterized by excessive or abnormal keratinization, either follicular or diffuse, even when the underlying inflammatory dermatosis does not in itself appear suitable for this form of therapy. Striking results were obtained with the administration of vitamin A in 2 cases of unusually hyperkeratotic lichen simplex chronicus in which other treatment had proved ineffective. Vitamin A therapy has also been of benefit in the handling of some forms of acne vulgaris.

The use of the vitamin B complex is recommended for the management of dermatoses in which allergic factors are involved. The beneficial effect may be due to the antichlorhydric fraction.

Cheilosis was formerly believed to represent uniformly a riboflavin deficiency, but it is emphasized that factors unrelated to vitamins, such as epithelial hypersensitivity and anatomic conditions, may be important in its genesis.

21 Shannon, W. R. Thiamin Chloride Aid in Solution of Mosquito Problem, *Minnesota Med* **26** 799-802 (Sept) 1943.

# NITRITOID REACTION FOLLOWING TRYPARSAMIDE THERAPY

## REPORT OF A CASE

LAURENCE J UNDERWOOD, M D

LOS ANGELES

Nitritoid reactions to tryparsamide were reported to be of rare occurrence for a time after the drug was first introduced for clinical use, but during the past few years increasing incidence of such reactions has been reported.<sup>1</sup> Moore<sup>2</sup> suggested that this increased incidence might be due to impurities in chemicals used in the manufacture of the drug and recommended that when reactions occur the type and lot number of the drug be reported to the appropriate manufacturer. Kopp and Solomon<sup>1a</sup> reported that during their first five years of experience with tryparsamide (1922 through 1926, inclusive) they observed a nitritoid reaction in only 1 patient but that the incidence had gradually increased until in 1939, of their patients receiving tryparsamide, 86 per cent exhibited some type of nitritoid reaction. Downs, McDermott and Webster<sup>1b</sup> reported that 30 (13 per cent) of 233 patients exhibited classic symptoms of nitritoid reaction and that 24 of them had the reaction after ten to one hundred injections. Beerman and Shaffer<sup>3</sup> observed four severe nitritoid crises among 16 patients manifesting some form of systemic reaction to tryparsamide. Other isolated cases have been reported by Silverston,<sup>4</sup> O'Leary and Becker,<sup>5</sup> Cormia,<sup>6</sup> Miller

and O'Donnell,<sup>7</sup> Astrachan and Franks,<sup>8</sup> Coon,<sup>9</sup> Ellis,<sup>10</sup> Levy,<sup>11</sup> Lehmann<sup>12</sup> and Zakon and Bluefarb.<sup>13</sup> During the interval from July 1941 through January 1944, a total of four thousand and twenty-one injections of tryparsamide were given in clinics of the Los Angeles County Health Department with the occurrence of only one nitritoid reaction, which is described in the case in this article.

Kopp and Solomon<sup>1a</sup> have reported that when such untoward reaction occurs, it usually is in patients showing other sensitivities, especially of the gastrointestinal tract, although including other indications such as chills, fever, fainting, weakness, dizziness, emotional upsets, drowsiness, and muscular tremors. Reactions were noted to occur in those who had received much tryparsamide, 76 per cent of reactions occurred in patients who had had more than thirty injections, while 17 per cent occurred in those who had received less than ten.

Kopp and Solomon,<sup>1a</sup> reporting on the untoward reactions to tryparsamide, stated that signs and symptoms may include sweating, flushing, pallor, cyanosis, coughing, sneezing, coryza, lacrimation, urticaria, pruritus, pain in the lower

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1 (a) Kopp, I, and Solomon, H C. The Untoward Reactions of Tryparsamide. *Am J Syph, Gonorr & Ven Dis* 24:265-283 (May) 1940. (b) Downs, W G, McDermott, W, and Webster, B. Reactions to Tryparsamide Therapy, *ibid* 24:16-21 (Jan) 1941.

2 Moore, J E. The Modern Treatment of Syphilis, ed 2, Springfield, Ill, Charles C Thomas Publisher 1933, p 125.

3 Beerman, H, and Shaffer, B. Reactions to Tryparsamide. A Review of Ten Years' Experience, *Brit J Ven Dis* 16:145-165 (July-Oct) 1940 abstracted, *Ven Dis Inform* 22:58-59 (Feb) 1941.

4 Silverston, I D. Tryparsamide Therapy in Neurosyphilis, *Lancet* 2:693-699 (Oct 2) 1926.

5 O'Leary, P, and Becker, S. Further Observations on Treatment of Neurosyphilis with Tryparsamide, *M J & Rec* 123:305-308 (March 3) 1926.

6 Cormia, F E. Allergy to Tryparsamide, Queries and Minor Notes, *J A M A* 106:1224 (April) 1936.

7 Miller, J K, and O'Donnell, H J. Sensitivity to Tryparsamide, *Arch Dermat & Syph* 35:264-266 (Feb) 1937.

8 Astrachan, G D, and Franks, A G. Nitritoid Reaction Following Injection of Tryparsamide, *ibid* 38:949-950 (Dec) 1938.

9 Coon, A B. Nitritoid Crises Following Tryparsamide Therapy, *ibid* 40:601-602 (Oct) 1939.

10 Ellis, F A. Nitritoid Reactions Due to Tryparsamide, *ibid* 40:707-708 (Nov) 1939.

11 Levy, H A. Nitritoid Reaction to Tryparsamide, *ibid* 41:690-691 (April) 1940.

12 Lehmann, H. Nitritoid Crises Following Injection of Tryparsamide, *Canad M A J* 45:129-130 (Aug) 1941.

13 Zakon, S J, and Bluefarb, S M. Prevention of Nitritoid Reactions Following Tryparsamide Therapy. *Urol & Cutan Rev* 46:435-436 (July) 1942.



part of the back, substernal discomfort, apprehension, difficulty getting breath, nausea, vomiting, diarrhea, weakness, collapse and convulsions. The pulse may be very weak with only a slightly increased or a rapid rate. The skin may be cold and clammy. The reaction is frequently ushered in by paroxysmal coughing during or immediately after the injection. Most allergic reactions occur within a few minutes after the drug is injected. Kopp and Solomon<sup>1a</sup> stated the possibility that the drug may act as a real chemical allergen after repeated injections. In 3 of their patients nitritoid crises were repeated with tryparsamide (a pentavalent arsenical) and with trivalent arsenicals. The reaction may be either mild or severe and may not follow the usual nitritoid symptomatic pattern. In some persons recovery is rapid, and in others collapse is severe, so that repeated administration of epinephrine is necessary. Most observers believe that treatment with tryparsamide should then be discontinued. If continued reactions occur, they may be more severe and with new manifestations. Nitritoid reactions have not been reported as occurring in patients in whom visual disturbances develop, furthermore, visual disturbances apparently did not occur, according to Kopp and Solomon,<sup>1a</sup> in the group of patients exhibiting a nitritoid reaction.

#### REPORT OF CASE

The patient, a married white American woman aged 49, was committed by the lunacy commission in May 1938 to the Norwalk State Hospital, where the diagnosis of psychosis with syphilis of the central nervous system was made. There had been no preceding history of or treatment for syphilis. The clinical picture was that of a deteriorated mentality, with hallucinations and delusions. The Wassermann reactions of the blood and spinal fluid were positive, the cell count of the spinal fluid was 45, it gave a 2 plus reaction for globulin, and the colloidal curve was not reported. While in the hospital, she had thirteen paroxysms and a temperature higher than 103 F for forty hours from inoculation with tertian malaria organisms. She also received ten injections of tryparsamide, 3 Gm each, without reported intolerance. She was paroled to relatives in December 1938.

The patient lapsed from treatment until she came to our clinic in November 1942 because of a small pruritic lesion on the hand. She had no other complaints. Apparently a fair remission had occurred from the neurosyphilis, although there was definite evidence of parenchymal damage. Physical examination was reported as revealing no significant abnormalities except pupillary changes and a blood pressure of 160 systolic and 90 diastolic. Visual examination by an oculist revealed slightly pale disks but normal periph-

eral fields. Kahn and Kolmer reactions of the blood were positive. Examination of the spinal fluid revealed Kolmer reaction,  $44 \pm 00$ , cells, 2, globulin, trace and colloidal benzoin curve, 00331133330XXXXX. She was given 1 Gm of tryparsamide. After the injection, shooting pains developed, radiating down both thighs and legs, and two days later diarrhea appeared. Within a few days she was admitted to the Los Angeles County General Hospital, and a diagnosis of probable pneumonia was made.

No further treatment was given until she came under my care in June 1943, at which time the Kahn and Kolmer reactions of the blood were positive. During the summer thirteen injections of bismuth subsalicylate in oil were given without toxicity. Next, 0.5 Gm of tryparsamide was given, and she had no signs of intolerance. A week later 1.0 Gm was tolerated without reaction. The following week, on Oct 11, 1943, while being given the tryparsamide injection slowly, she became stuporous, dyspneic with slight wheezing and flushed in the face and neck, the conjunctiva was injected, and sweating was profuse. She vomited only a small amount of mucus. The injection was immediately discontinued, about 1 Gm of the 2 Gm dose had been given, and 0.5 cc of a 1:1,000 solution of epinephrine hydrochloride was given subcutaneously and repeated in fifteen minutes. She recovered within about ten minutes, and the blood pressure and pulse were not grossly abnormal. She left the clinic in about forty-five minutes and the next day felt completely recovered. After the injection, there was hypermenorrhea during her next period and amenorrhea the following month, both unusual symptoms for this patient. There were no visual disturbances.

Three weeks after the first reaction, with no preparatory medication, 1 Gm of tryparsamide was given very slowly. She felt well before and during the injection. About one minute after the injection was finished, she stated that she felt as though she were going to faint. Symptoms and signs were similar to those previously manifested. However, she did not vomit and was in a semicomatose condition for less than five minutes. The pulse was regular (rate, 48) and of good quality, the blood pressure was 150 systolic and 90 diastolic, and fifteen minutes later the pulse rate was 84. She was placed in a horizontal position and given 5 minims (0.31 cc) of epinephrine followed by a similar dose after fifteen minutes. Within five more minutes she had recovered sufficiently to walk to another room, where she rested for about one hour. She appeared to be in a satisfactory condition except for a mild transitory amnesia. During the next two days she complained of paresthesias in the form of electric-like pains in the feet and calves, and had two watery bowel movements on the second day. Four days later she noticed a small dry red pruritic patch on the dorsum of the right hand, possibly a fixed drug eruption, which persisted for about one month and gradually disappeared during the use locally of boric acid ointment.

Further treatment has consisted of injections of bismuth subsalicylate, potassium iodide given orally and the trivalent arsenicals mapharsen and neoarsphen-

amine, with no signs of intolerance. Use of tryparsamide has been discontinued permanently. Visual examination by another oculist during December 1943 revealed no abnormalities of the disks, fundi, visual fields or acuity. Blood counts and urine were normal. Serologic tests of the blood and examinations of the spinal fluid made in December 1943 and June 1944 gave essentially the same results as in November 1942. A patch test with tryparsamide elicited a negative reaction in February 1944. At the present time, physical examination reveals pupillary abnormalities and patellar and ankle reflexes absent bilaterally. Roentgenographic, fluoroscopic and cardiac examinations indicate possible uncomplicated aortitis.

The patient now has no complaints and feels well, although she has definite changes in personality, revealed by her moderately incoherent, rambling conversation and a moderate impairment of memory. Her husband states that he has noticed gradual improvement in her mental condition since 1939, and that she is able to do the simple household tasks.

#### SUMMARY

Repeated intolerance to tryparsamide manifested in nitritoid reactions and a possible fixed drug eruption occurred in a patient approximately five years after tryparsamide was first given, and after a total of fourteen injections, three in the present course, had been given.

The patient has exhibited no evidence of intolerance to the trivalent arsenicals to date.

Although the incidence of nitritoid reactions to tryparsamide has been reported to be increasing, the case reported is the first in which they have occurred in a patient of the social hygiene clinics of the Los Angeles County Health Department, which has given a total of four thousand and twenty-one injections. In these clinics, tryparsamide is used with the usual precautions in selected cases of neurosyphilis.

## SPREAD OF DERMATITIS VENENATA BY VESICLE CONTENTS

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CAMDEN, N J

PHILADELPHIA

There is a belief commonly held by the public and by some physicians that the liquid content of the vesicles of dermatitis venenata due to poison ivy is capable of producing new lesions and may even cause an eruption to appear on other persons contaminated by the vesicle liquid. Based on our clinical impressions over a period of years, the principles taught in the outpatient department at the Jefferson Medical College have been contrary to this view. In 1937-1938 patch tests<sup>1</sup> with various strengths of poison ivy extracts were performed on 223 young men. There were positive reactions to 156 patch tests on 101 men. Many of these reactions were vesicular. These men were advised not to apply lotions or otherwise treat the positive test sites or in any way prevent the vesicle contents from being casually transferred to other parts of the skin. In no instance did we observe any lesion developing outside the original test site. The subjects were kept under observation for four weeks after the performance of the tests. This was interpreted to mean that the vesicle liquid was unlikely to spread the eruption by chance or induction.

In order to obtain more direct proof, in September 1943 we began to apply patch tests with a poison ivy extract<sup>2</sup> to another group (87) of young men. Seventeen of the men whose reactions were of the vesicular type were further utilized in an experiment in which vesicle fluid was transferred from the affected arm to the other arm, following the technic used in making patch tests. All these tests elicited negative results. Fourteen other men whose reactions in the primary test were of the vesicular type transferred the vesicle liquid in the form of a patch test to the unaffected arm, and, in addition, each used the vesicle liquid for a patch test of another person with a history of susceptibility to ivy dermatitis. One of the men in the original group had a positive reaction to the fluid from his own vesicle seven days after the test was applied. All

the transfers to other persons produced negative results.

One student who reacted with vesiculation to the ivy extract had no reaction to the test with his own vesicle liquid, but a group of vesicles developed on the forearm on an area which had come in contact with the primary test site when the elbow was fully bent. The effect of this unintentional transfer appeared two days after the covering of the primary patch was removed.

In addition to the men in whom lesions had been produced experimentally by patch tests with the poison ivy extract, 10 men in whom dermatitis venenata (poison ivy) naturally occurred were added to the series. The eruptions were of recent origin, with unopened vesicles or blebs. Without being cleansed the lesions were punctured with a clean hypodermic needle and the contents used for a patch test on an unerupted area of skin. All the tests elicited negative results.

These results agree in the main with those of Sulzberger and Katz,<sup>3</sup> who obtained no positive reactions to patch tests with the liquid from the tops of vesicles produced by war gases and by poison ivy extract. However, we observed positive results (1 unintentional) indicating that in a certain small percentage such effects can be produced.

In our 2 positive transfers there was a chance that the poison ivy extract contaminated the vesicle liquid. The surface of the vesicles of the positive patch reactions was not cleaned in any way before the vesicle liquid was obtained and it is possible that some of the original ivy extract was still on the surface of the lesion. This omission of cleansing was intentional.

### CONCLUSION

The vesicle liquid of dermatitis venenata caused by poison ivy is not ordinarily capable of producing new lesions on the victim or on persons contacted by him.

516 Cooper Street  
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3 Sulzberger, M B, and Katz, J H. Absence of Skin Irritants in Contents of Vesicles, *U S Nav M Bull* 41 1258-1262 (Sept) 1943.

1 Knowles, F C, Decker, H B, Pratt, A G, and Clarke, J A, Jr. Susceptibility of Allergic and Nonallergic Persons to Rhus Toxicodendron, *Arch Dermat & Syph* 38 773-779 (Nov) 1938.

2 Ivy extract obtained from Arthur Coca, MD

# PRIMARY TUBERCULOUS COMPLEX OF THE SKIN

OCCURRENCE IN A WOMAN AGED SIXTY-FOUR

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SAN FRANCISCO

The primary tuberculous complex of the skin, although rare in dermatologic experience, is a well established clinical entity. The literature on this subject has been adequately reviewed, by Stokes<sup>1</sup> in 1925, by Michelson<sup>2</sup> in 1935 and by O'Leary and Harrison<sup>3</sup> in 1941. As these papers are so complete no attempt will be made to present the subject in detail.

The purpose of this paper is to report the case of an elderly woman who presented the clinical picture of the primary tuberculous complex of the skin. While the literature already contains a sufficient number of cases which satisfactorily describe the clinical features of this type of inoculation tuberculosis, the case reported here is of such an unusual character as to be worthy of discussion.

The primary tuberculous complex of the skin as summarized by Bruusgaard<sup>4</sup> consists of a series of clinical events which follow the introduction of tubercle bacilli into the skin of an individual previously free of tuberculosis. A small indolent inflammatory nodule or ulcer appears from one to three weeks after the inoculation. Four to ten weeks later regional adenitis with or without lymphangitis, follows. The adenitis is the most striking feature of the disease. The lymph node adjacent to the primary lesion enlarges and then, by extension, other nodes become involved. At first the nodes are

firm and discrete but within a few weeks they undergo caseation necrosis, they soften, and the skin over them becomes erythematous. Eventually they rupture through the skin, forming draining sinuses. A periadenitis develops, matting the nodes together, thus producing extensive indurated inflammatory masses. As a rule the disease is comparatively benign, and the process heals within a few months. However, it may extend to other groups of lymph nodes and thus remain active for months or years. Generalized tuberculous infections, including pulmonary lesions, may follow.

The primary lesion is usually small and insignificant as compared to the massive adenitis. At times, however, the primary ulcer may attain a considerable size. Frequently healing is not complete, and small lupus nodules persist in the skin around the site of the original lesion.

The reaction to the tuberculin test becomes positive within one to six weeks after the inoculation with the tubercle bacillus.

## THE CONCEPT OF THE PRIMARY TUBERCULOUS COMPLEX OF THE SKIN

The primary tuberculous complex represents the reaction of the tissues of a tubercle-free organism to inoculation with the tubercle bacillus. As Goldsmith<sup>5</sup> has pointed out, Koch in 1891 was the first to demonstrate the phenomenon of allergy to the tubercle bacillus. He demonstrated that when the normal guinea pig is inoculated through the skin with tubercle bacilli symptoms described as the primary cutaneous tuberculous complex ensue. When the animal is reinoculated several weeks later, an intense inflammatory reaction occurs locally which heals rapidly without adenitis. While the primary tuberculous complex is fairly consistent in its course in man the symptoms which follow reinoculation of tubercle bacilli into the skin months or years later are not always as uniform. The reaction which will occur depends as

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1 Stokes, J. H. Primary Inoculation Tuberculosis of the Skin with Metastasis to Regional Lymph Nodes, *Am J M Sc* **169** 722-736 (May) 1925.

2 Michelson, H. E. The Primary Complex of Tuberculosis of the Skin. Review of the Literature, *Arch Dermat & Syph* **32** 589-601 (Oct) 1935.

3 O'Leary, P. A. and Harrison, M. W. Inoculation Tuberculosis, *Arch Dermat & Syph* **44** 371-390 (Sept) 1941.

4 Bruusgaard, E. The So-Called "Primary Complex" of Tuberculosis in the Skin, *Brit J Dermat* **46** 113-126 (March) 1934.

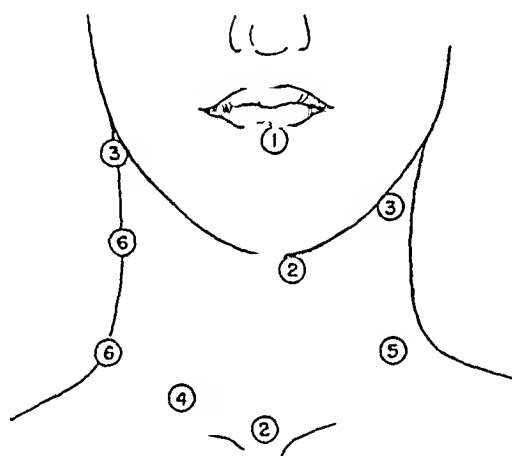
5 Goldsmith, W. N. Recent Advances in Dermatology. Philadelphia, P. Blakiston's Son & Co., 1936, p. 273.

Stokes<sup>1</sup> stated, on the almost unlimited possible combinations existing between the susceptibility of the host and the virulence of the infecting bacilli. Under these conditions tuberculosis verrucosa cutis, verruca necrogenica, lupus vulgaris, tuberculous ulcers or scrofuloderma may develop. At times adenitis and lymphangitis accompany these lesions, thus simulating the primary complex closely.

Ghon's<sup>6</sup> description of the primary tuberculous complex of the lung did much to clarify the clinical significance of this condition. Bruusgaard<sup>4</sup> later showed that the skin may act as the portal of entry for the primary inoculation of the tubercle bacillus, producing a clinical picture analogous to that of the primary tuberculous complex of the lung. Both Ghon and Bruusgaard believed that the primary tuberculous complex could occur only in individuals who had

lesion from other eruptions occurring in patients previously inoculated. It has been emphasized repeatedly that reinoculation tuberculosis may so closely simulate the primary tuberculous complex of the skin as to be indistinguishable from it. It may be impossible to establish this diagnosis in adults, particularly those of advanced age.

If identical reactions to the inoculation of tubercle bacilli can be evoked in individuals who have previously been infected with tubercle bacilli and in those who have not, then the basis for the conception of the primary tuberculous complex must be broadened. The premise on which the theory of the primary tuberculous complex is founded is that these reactions occur only in previously noninfected persons. It is accepted generally that patients may recover completely from a primary tuberculous infection.



#### DEVELOPMENT OF LESIONS CHRONOLOGICALLY

①, ②, ③, ④, ⑤, ⑥ Represent enlarged lymph nodes, abscesses and draining sinuses

① Primary ulcer (March, 1941) developed 7 months before entry to the hospital

②, ② Developed (May, 1941) 6 weeks after the primary onset

③, ③ Developed (July, 1941) 3 1/2 months after the primary onset

④ Developed (August, 1941) 4 1/2 months after the primary onset

⑤ Developed (Sept., 1941) 6 months after the primary onset

⑥ Developed (October, 1941) 7 months after the primary onset

(Admitted to hospital 10/28/41)

Fig 1—Diagrammatic sketch illustrating the chronologic development of the lesions

not been previously infected with tuberculosis. However, they made the reservation that this statement was not incontestable, since all the facts concerning tissue reaction to the tubercle bacillus are not known.

Michelson suggests that, in order to avoid confusion, rigid criteria should be adhered to in establishing a diagnosis of the primary tuberculous complex. He stated that a diagnosis of primary tuberculous complex of the skin is not acceptable unless it can be demonstrated that the patient did not have tuberculosis previous to the onset of his clinical lesions. In such cases the tuberculin test must have been negative before the onset of the disease. He, as well as many other authors, reiterate the difficulty of differentiating clinically this type of

and, especially in late adult life, lose all evidence of allergy to the tubercle bacillus. These persons would then become candidates for a second primary tuberculous infection of the skin.

#### REPORT OF A CASE

*History*—J. K., a white married woman aged 64, entered Mount Zion Hospital, San Francisco, Oct 28, 1941, on the recommendation of Dr. Franklin I. Harris, because of a small ulcer on her lower lip. She also presented several masses and sinuses on both sides of her neck. She stated that the lesion on the lower lip had developed seven months previously. Shortly before its appearance she had been kissed violently by her husband, who was delirious at the time because of a terminal generalized tuberculous infection. Autopsy of the husband revealed tuberculosis of the lungs, liver, spleen and lymph nodes. Tubercle bacilli were demonstrated in a large cavity of the lower lobe of the left lung. Histologic examination of the affected tissues showed a characteristic tuberculous structure, with caseation necrosis, epithelioid cells and giant cells.

6 Ghon, A. Einiges zum primären Komplex bei der Tuberkulose, Beitr. z. path. Anat. u. z. allg. Path. 69: 65-71, 1921.

The ulcer on the cutaneous surface of her lower lip appeared about two weeks after the kiss. She was unable to remember if she had an abrasion or wound on the lower lip at the time of the inoculation. This lesion persisted until about three weeks before her entry to the hospital. At this time it had healed, but the site remained purplish red and was moderately indurated. Six weeks after the appearance of the sore on the lower lip, two nodules appeared, one in the submental and the other in the right supraclavicular areas. These enlarged rapidly, the overlying skin reddened, the masses softened and eventually opened to the surface to discharge purulent material. During the next five months similar nodules appeared in other areas of the neck (fig 1).

There were no complaints other than the loss of 42 pounds (19.1 Kg) in the past six months. She denied cough, sputum, hemoptysis, chills or fever, sweats and malaise. There was no history of tuberculosis in her parents. She had been married twice. One son was living and well at the age of 45. She was born in

purulent material. The ulcers were fungating and undermined and led to sinuses deep in the subcutaneous tissues. The process caused large areas in the neck to be indurated and fixed. Figure 2 illustrates the location of the lesions.

Physical examination revealed no significant findings except those previously described.

**Laboratory Findings**—The urinalysis gave normal results. The blood count showed 71.8 per cent hemoglobin (equalling 11 Gm), 4,440,000 red blood cells, 8,700 white blood cells, 75 per cent polymorphonuclear neutrophils, 22 per cent lymphocytes, and 3 per cent monocytes, 79 per cent of the neutrophils were filamented and 21 per cent were nonfilamented. The Wassermann and Kahn reactions were negative. Roentgenograms of the chest and mandibles were negative for tuberculosis. The reaction to the coccidioidin test was negative. The Frei test gave negative results. The tuberculin test, 1:1,000, showed a strongly positive reaction (The patient had not had a tuberculin test previously). The complement fixation

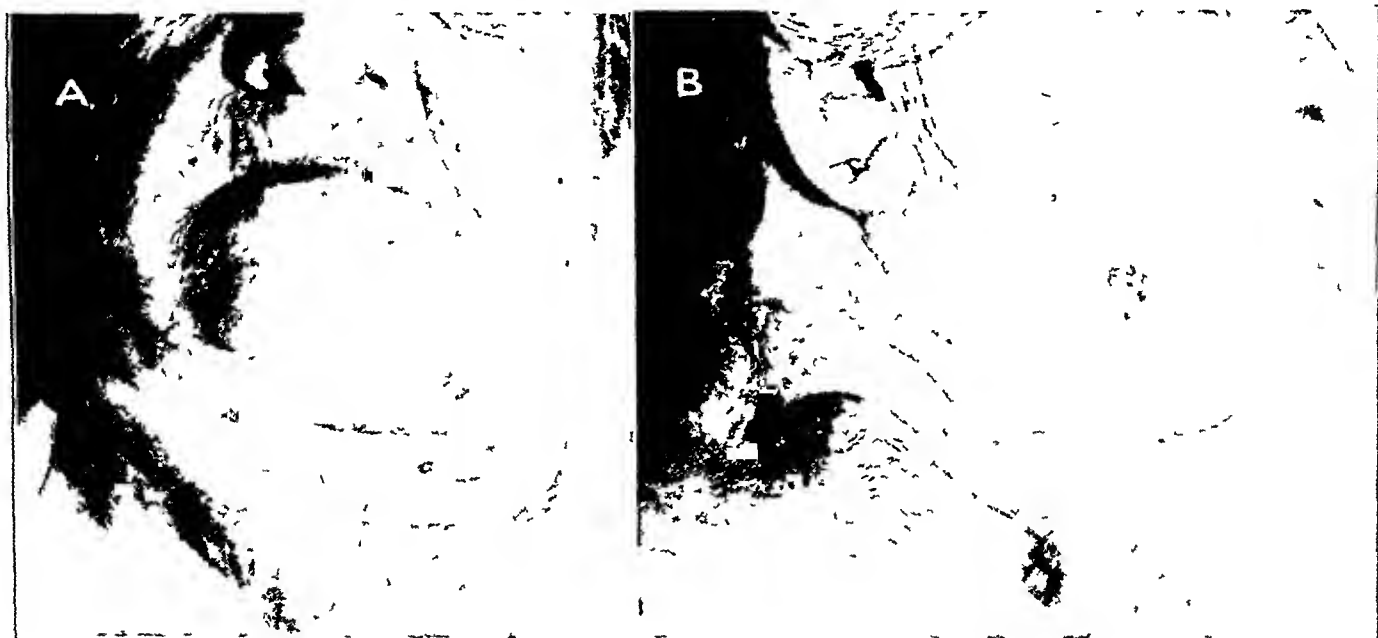


Fig 2—A, front and B, right side of patient's face on Oct 29, 1941

Buenos Aires, had lived in France and for the past fifty-four years had lived in San Francisco. She had worked in the following types of establishments: tailor shop, thirty-five years; sheep ranch, three years; housework, eight years; and grocery store for the last five years. Her habits as to diet, rest, alcohol and tobacco were normal.

The patient had consulted several physicians previously. Shortly before entry, she had been studied by Dr. H. E. Miller who had taken a biopsy specimen from the lesion on the lip and had inoculated a guinea pig with pus from an abscess in the neck.

**Examination**—Physical examination revealed a woman 64 years of age in fair nutrition and apparently well except for the local condition of the lower lip and neck. On the lower lip there was a depressed scar about 1 cm. in diameter, moderately indurated and purplish red. This lesion for the most part involved the glabrous skin of the chin and encroached slightly on the vermillion border of the lip. In the submental, both submaxillary and both supraclavicular triangles of the neck were reddish indurated masses varying in size from that of a lima bean to that of a small hen's egg. Many of these lesions were ulcerated and were draining

test for psittacosis was positive in a dilution of 1:2. Smears from pus taken from an abscess of the neck were positive for acid-fast bacilli.

A biopsy specimen was taken from an abscess of the neck on Oct 29, 1941 (by Dr. F. I. Harris). The pathologic report by Dr. G. Y. Rusk was as follows: "Microscopic examination of sections of the tissue shows most of it to have undergone caseous necrosis (fig 3). In the peripheral portions, however, there are some areas composed of epithelioid cells and lymphocytes. A fine fibrous stroma can be distinguished. In a few regions some large multinucleated giant cells of the Langhans type are present."

An inoculation was made into a guinea pig on Oct 29, 1941. The pig was killed on Nov 24, 1941, and was found to have tuberculosis.

A biopsy specimen of the lesion of the lip had been taken by Dr. H. E. Miller (fig 4). This section did not show caseation necrosis. There were numerous epithelioid cells and an occasional giant cell of the Langhans type. There were also scattered lymphocytes. Acid-fast stains of the sections failed to reveal acid-fast bacilli. The histologic structure was that of an early tuberculous lesion.



A guinea pig inoculated by Dr Miller at the University of California Hospital showed tuberculosis

The patient's temperature, pulse and respiration were normal throughout her stay in the hospital. She was discharged on Nov 3, 1941

*Subsequent Course*—The patient was referred to Dr William Voorsanger, who treated her in a tuberculosis sanatorium. She remained there until July 1942, and received treatment with tuberculin, ultraviolet radiation and a small amount of roentgen ray radiation. Her temperature remained below 100 F and for the most part ranged between 98.6 F and 99.4 F. The patient gained 8 pounds (3.6 Kg) in weight and showed considerable improvement. The lesions in the neck healed almost completely

shown in the film made March 23, 1943. At this time, the diaphragm is smooth and not elevated. There is a general haziness over the left thoracic cage, which may be due to pleural thickening. Extending from the hilus of the left lung and involving the apex, first, and to a lesser extent the second interspace, there is a dense infiltration. It occupies the posterior aspect of the left upper lobe. The density has a rather homogeneous character for the most part, although the lower border is somewhat less distinct.

"The trachea is not shifted and there is no mediastinal deviation. No cavities are seen within the area of consolidation. Conclusion: The lesion of the left upper lobe is exudative in character. Tuberculosis is a distinct possibility. These films were examined also by

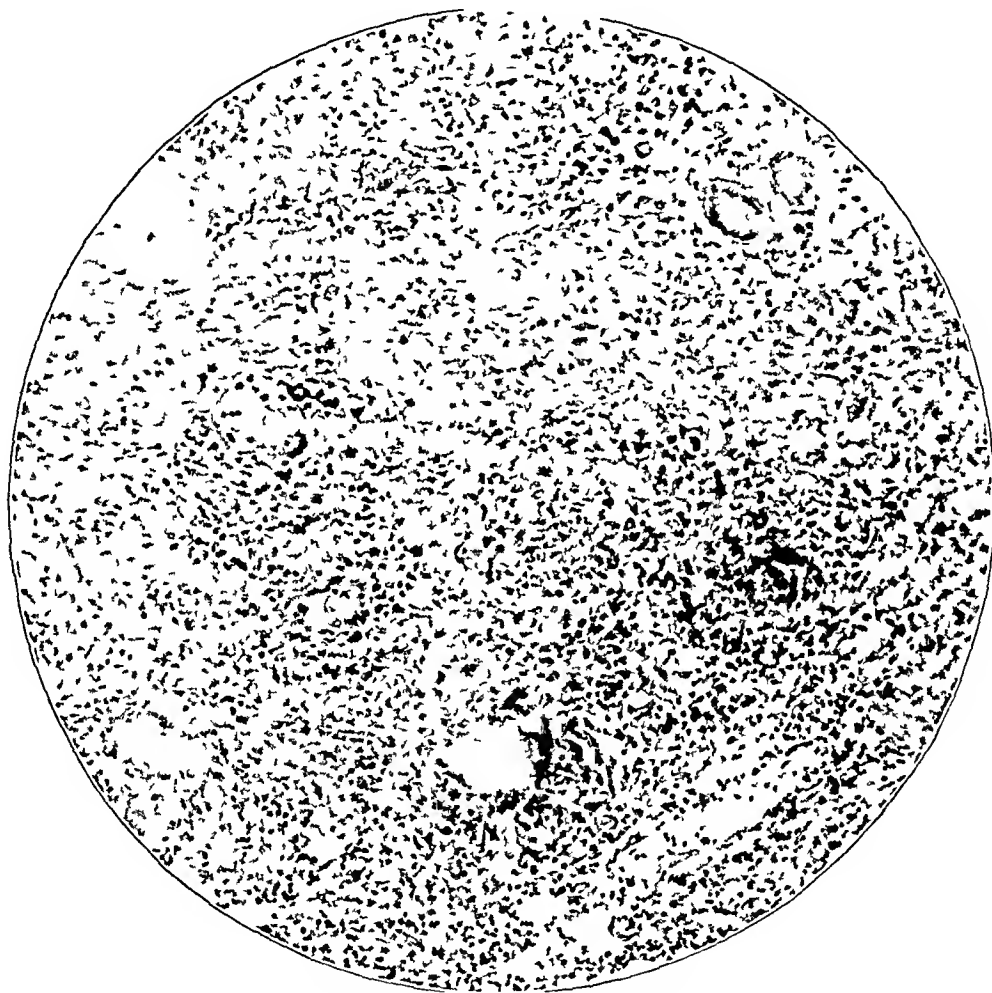


Fig 3—Photomicrograph of abscess of neck, Oct 29, 1941,  $\times 43$

Between July 1942 and March 1943 the patient was ambulatory. During this interval she lost 20 pounds (9.1 Kg). At this time the sputum was negative for tubercle bacilli. The left breast was swollen and reddened. The patient was coughing considerably. She was last seen by Dr Voorsanger on April 12, 1943. Roentgen ray examination of the lungs was made in March 1943. These plates were examined by Dr Helen Weyrauch and compared with films of the chest taken on Oct 29, 1941. Her report was as follows: "Film of the chest made Oct 29, 1941 shows nothing of significance except small calcifications at the hilum, these are chiefly seen at the right hilum. These same calcifications are seen on the film made in 1943 and apparently have not changed. These calcifications signify healed primary tuberculosis. Considerable change is

the roentgen ray department of the University of California, and a similar opinion was given. The appearance, however, would be consistent with most any type of consolidation" (fig 5).

The patient was seen last by me on May 8, 1944. The lesion of the lip had entirely disappeared except for a small depressed scar. There were no papules, nodules or other lesions suggesting lupus vulgaris. A few of the original abscesses and sinuses had healed, but the process had extended considerably. The supraclavicular areas on each side were infiltrated massively, and several sinuses were present. Pus was exuding from the sinuses. On the right, the process involved the postauricular lymph nodes, and a sinus was present here also. The lymph nodes of the left axilla were inflamed and matted together. Pus exuded from sev-

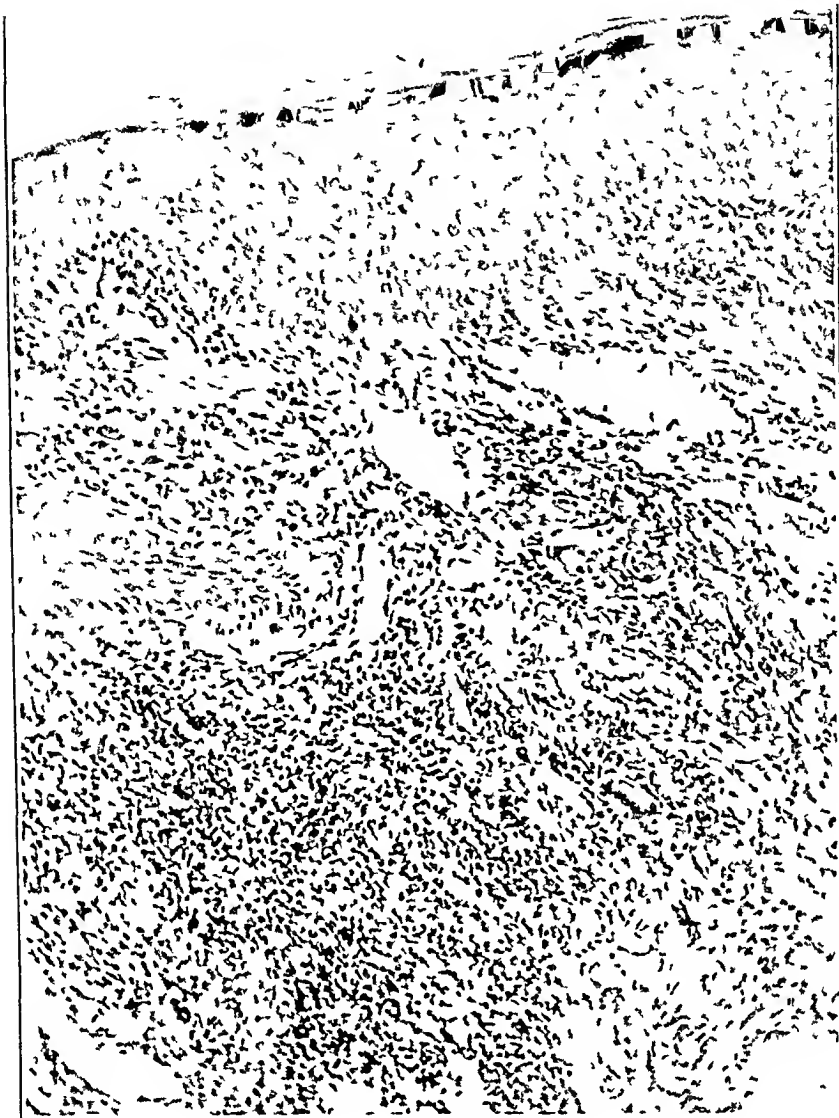


Fig 4—Photomicrograph of lesion on lower lip, July 20, 1941,  $\times 43$

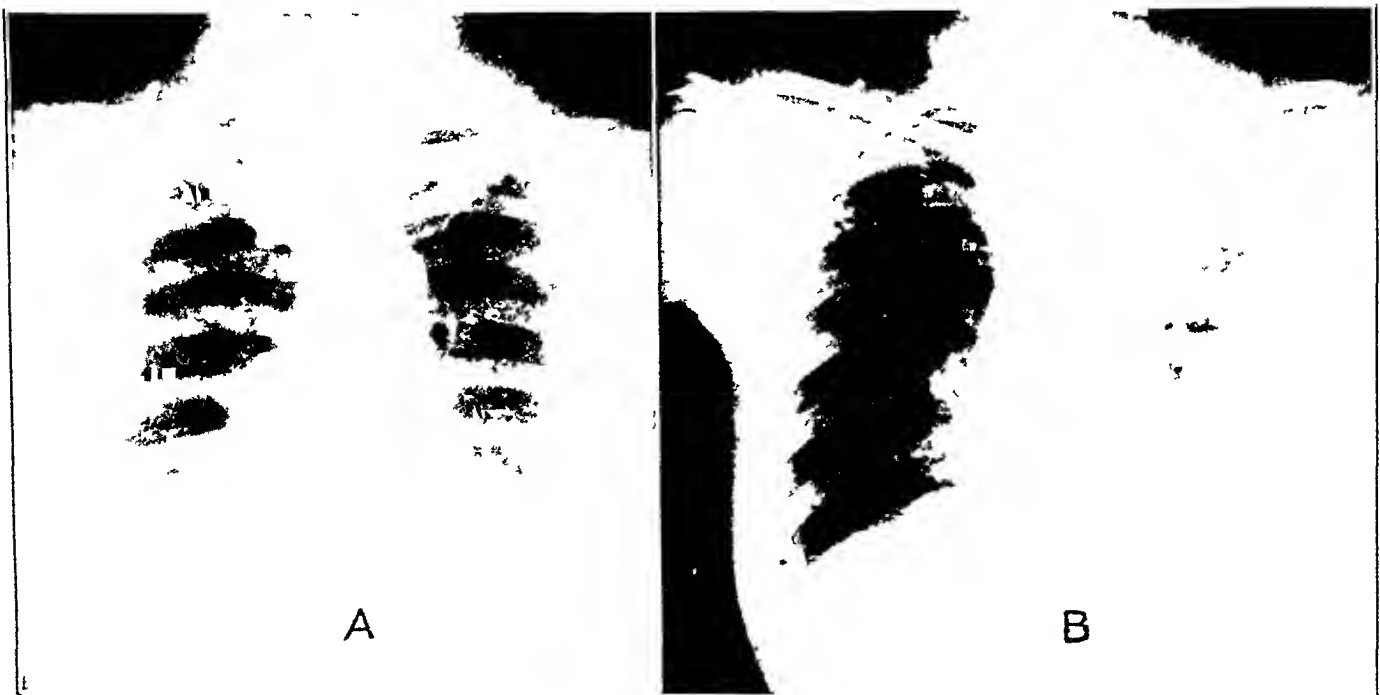


Fig 5—*A* roentgenogram of chest on Oct 29 1941 showing calcium deposits at the hili. There are no evidences of an active inflammatory process. *B* roentgenogram of chest in March 1943, showing the right side unchanged while an extensive inflammatory process has appeared on the left side

eral openings. The left breast was also involved. The skin over the sternum was reddened and indurated and a large punched-out ulcer was present over the lower portion. This entire process gave the appearance of an extensive scrofuloderma with ulceration (fig 6).

Between March 1943 and May 1944 she had gone downhill, becoming progressively cachectic. There was a daily afternoon rise of temperature to 99.6 F.

The patient died on June 2, and an autopsy was performed by Dr. H. Gifford of the pathology department of the University of California. He reported the following anatomic diagnosis: (A copy of the complete post-mortem observations will be forwarded to the reader if desired.)

#### I Tuberculosis

##### A Skin

##### B Multiple sinus tracts, left thorax

##### 1 Fibrous adhesions, left pleura

##### C Tuberculous pneumonia, left lung

##### 1 Hydrothorax on the left side

##### D Miliary tuberculosis of both kidneys

#### II Fat infiltration of the liver



Fig 6—Appearance of axilla on May 8, 1944

#### SUMMARY OF CLINICAL FEATURES OF THE CASE

A 64 year old woman became inoculated with virulent tubercle bacilli when kissed by her husband dying of tuberculosis. The rapid appearance of the tuberculous lesion on the lower lip followed within five or six weeks by cervical adenitis and the subsequent involvement of other nodes on both sides of the neck with caseation necrosis fulfil the criteria for the primary tuberculous complex of the skin. The clinical course of the disease remained benign until one year before death. Other chains of lymph nodes later became involved and finally symptoms of pulmonary tuberculosis appeared. The pulmonary lesions followed the cutaneous infection and were probably due to direct extension from the skin into the pleural cavity. The intradermal tuberculin reaction was strongly positive at the time of first observation, that is, seven months after the onset of the disease. There was no history of

a previous tuberculin test. Inoculation of a guinea pig and bacteriologic and histologic studies of the affected tissues confirmed the tuberculous nature of the infection.

#### COMMENT

This patient presented clinical and pathologic findings identical with those seen in the primary tuberculous complex of the skin. There was, however, definite roentgen ray evidence of a healed primary tuberculous complex of the right lung. This early infection apparently occurred many years before, probably in childhood. Post-mortem examination of the right lung and hilar regions failed to show, grossly, the presence of healed tuberculosis. The examining roentgenologists insisted that the roentgen ray evidence was incontestable and that a minute microscopic study of the organ would reveal healed lesions of tuberculosis.

This case does not fulfil the criteria for a diagnosis of the primary tuberculous complex as laid down by Blumenthal.<sup>7</sup> It must be regarded, therefore, as one of reinfection tuberculosis with a clinical and pathologic picture identical with a true primary tuberculous complex of the skin. The concept of the primary tuberculous complex is based on the fact that tissues react in a different manner to an original inoculation with the tubercle bacillus than to subsequent inoculations. Although the patient reported herein had had tuberculosis earlier in life, her tissues responded to a later inoculation in an identical way, as is seen in the true primary tuberculous complex of the skin. The concept of the primary tuberculous complex should be broadened to include reinfections of this type. In this case the first primary tuberculous complex occurred in the lung and was completely healed. The inoculation sustained later in life led to a second primary tuberculous complex, but this time the site of the infection was the skin. An analogue to this is seen in syphilis from which a person may be cured of a primary infection with *Treponema pallidum* and then a second primary lesion may develop on reinfection. Reinfection in syphilis is regarded as evidence of cure and may possibly have the same significance in tuberculosis.

The advanced age of the patient is a striking feature of this case and brings up certain points for discussion. There is an agreement among investigators of tuberculosis that the number of persons who reach adult life without having contracted a tuberculous infection is constantly

<sup>7</sup> Blumenthal, F. *Allgemeine Betrachtungen über die Hauttuberkulose*, *Ergebn d ges Med* 19: 235-258, 1934.

increasing. It is certainly possible for a person to attain old age without having had tuberculosis. The exact incidence of tuberculosis in the population is not known but estimates do not exceed 90 per cent, even for the aged. Amazon<sup>8</sup> showed that people may reach an advanced age without showing evidence of tuberculosis, clinically, roentgenologically or by the tuberculin test. He studied a group of 619 Jewish men and women, who had lived under crowded conditions from early childhood and who undoubtedly had been exposed repeatedly to tuberculosis. They varied in age from 65 to over 80. Twenty-six per cent showed negative reactions to 0.1 mg of old tuberculin and gave no clinical evidence of tuberculosis. Of them, 64 per cent did not have any signs of tuberculosis on roentgen examination. It is logical to assume that a majority of those who gave negative reactions to tuberculin probably had had tuberculosis some time in their lives but had spontaneously eradicated the infection and had become insensitive to tuberculin.

The clinical course of this patient's tuberculosis was unusual in its long duration and the progressive involvement of many chains of lymph nodes. The ulceration over the sternum, the involvement of the left breast and finally the extension of the process into the chest were striking features. The primary tuberculous complex of the skin is usually benign in its course, and the process heals within a few months. However, generalized infections do occur. In this case it is probable that the patient's age contributed to her inability to stop the advance of the infection. Rich<sup>9</sup> points out that resistance to tuberculosis is definitely decreased in the aged.

#### SUMMARY

A woman aged 64 showed the clinical features of the primary tuberculous complex of the skin.

The patient showed evidence of healed tuberculosis of the lung. She later contracted a tuberculous reinfection with symptoms identical with the primary tuberculous complex of the skin.

The advanced age of this patient and the clinical course of her disease were unusual features.

#### ABSTRACT OF DISCUSSION

DR HENRY E. MICHFSON, Minneapolis. This is a most interesting case report and it interests me because it allows one to speculate on the course of events and to evaluate the facts as found. I do not believe that

<sup>8</sup> Amazon P. Tuberculin Reaction in Old Age, *Am Rev Tuberc* 47:41-45 (Jan) 1943.

<sup>9</sup> Rich A. R. The Influence of Age-Determined Factors on the Development of Tuberculosis. *Minnesota Med* 21:745-763 (Nov) 1938.

we need to quibble about the name. The important thing is that the patient had a primary cutaneous lesion after which many other lesions developed, and the disease terminated in the death of the patient.

It would be hard for me to believe that a positive reaction to the tuberculin test did not develop, since she lived with her husband for many years while he had severe tuberculosis, which ended in death. My experience in the sanatoriums has shown that interns and nurses, even though they do not get the disease, almost always have positive reactions to the tuberculin test. When a person is inoculated with tuberculosis the resistance is what counts, and evidently this patient had good resistance but high allergy developed at the time of her inoculation. Had she had poor resistance at the time the lesions would not have healed. There is a long interim between the lesion and the adenitis and one wonders whether or not the bacilli migrated from the lip to the glands or were brought to the glands by the blood stream. The first roentgenogram I believe shows some infection, for one must not look on calcification as a cured lesion since the body chemistry can often dissolve calcium, and living bacilli have been found inside of a calcified gland. I do not believe that the extension was from the skin into the lung. This would be most unusual. I believe the woman was hoarding many bacilli. Her resistance was dropping rapidly and many foci developed. One must never speculate from terminal events because one cannot trace backward just what took place.

DR A. BENSON CANNON, New York. We are indebted to Dr Epstein for calling our attention to a condition that is apparently rare and seldom recognized. A few years ago I observed a medical student suffering from indolent ulcer of the right index finger, this was followed by a lymphangitis extending up the forearm and arm and an enlarged gland of the right axilla. He had been studied by a number of competent physicians and a diagnosis of syphilis, tularemia or staphylococcal infection had been made. An agglutination test for tularemia was negative. A biopsy specimen from the ulcer on his finger showed the structure of tuberculosis and a portion injected into a guinea pig produced tuberculosis in the animal. A second patient, a pathologist making postmortem examinations, I saw in consultation about a year ago with an ulcer just above where his glove fitted on his forearm, with lymphangitis extending to the axilla and also enlarged glands draining into the axilla. In this case, too, tuberculosis was proved to be present by biopsy and by guinea pig inoculation. Excision of the primary sore and the enlarged glands draining the sore was done in each case, with a complete and apparently permanent cure.

Based on the apparent cure obtained by surgical removal of the primary lesion and the adjacent enlarged glands in the 2 cases cited, and the similar beneficial results that I have observed in other cases in which isolated lesions of tuberculosis were extirpated, I can't help wondering if Dr Epstein's patient had been treated surgically in the same way whether a favorable result might not also have been effected. It seems to me that complete surgical removal of the affected tissue in these cases is the treatment of choice.

DR CHARLES C. DENNIE, Kansas City. An 18 year old youth at the University of Missouri about twenty-one years ago joined the Reserve Officers Training Corps. Many of the boys decided that they would have their arms tattooed which he also did. The tattooer was an old-time tattooer and wet the needle with his lips.

The youth came to me about six weeks later with an indurated ulcer. Of course, I examined it by dark field

and took a culture of it. Nodules began going up the arm, which exactly imitated sporotrichosis.

I aspirated the glands and planted the material on a medium to determine whether *Sporothrix* was present. When none were cultivated I took one of the glands and inoculated it into two guinea pigs. Both of the guinea pigs showed generalized involvement with tubercle bacillus. This case is an instance in which infection proceeded through the subcutaneous lymph glands into the arm.

I do not know whether the patient had tuberculosis of the lungs before that. His father had, because I treated his father for tuberculous sinuses in the back of his head. Nevertheless, military tuberculosis of the lungs developed and he was in our state sanatorium at Mount Vernon for over two years.

Last year he came into the office again, almost twenty years after the primary inoculation, with a breakdown at the site of these glands under his arms, which a few doses of roentgen rays cured.

Owing to my or his negligence his lungs were not investigated at that time, nor were they examined before he received this inoculation tuberculosis.

DR NORMAN N. EPSTEIN, San Francisco. I wish to thank the discussers for their instructive discussion, and

particularly Dr. Michelson. I did not expect the presentation to be accepted without qualification.

The point that I should like to make is that, according to the literature, the primary tuberculous complex consists in a primary lesion occurring at the site of inoculation of tubercle bacilli followed within four, five or six weeks by suppurative adenitis. This series of clinical events occurred in this patient. Since she had a lesion on the lower lip followed by enlargement and suppuration of the submental lymph node five or six weeks later, it is logical to assume that the lesion on the lip and the lymphadenopathy were part of a common disease process.

The further clinical course of these lesions, which changed to large ulcerations and scrofuloderma, was dependent on those factors which control every tuberculous infection, namely the resistance of the host and the virulence of the infecting organisms.

The fact that this woman was the wife of a man who died of tuberculosis does not necessarily indicate that she had been infected by him long before the appearance of the lesion on her lip. He had become acutely ill with tuberculosis and was hospitalized shortly thereafter.

Dr. Cannon has made a good point. Prompt surgical treatment of this patient may have prevented the spread of the tuberculosis.

# KAPOSÍ'S SARCOMA AND LYMPHATIC LEUKEMIA

## REPORT OF A CASE WITH HISTOLOGIC EVIDENCE OF THE TWO DISEASES IN THE SAME LESION

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AND

MARGARET GRAY, B A

NEW YORK

Cole and Crump,<sup>1</sup> in 1920, reported 2 cases of Kaposi's sarcoma, in 1 of which it was complicated with lymphatic leukemia. A case of Kaposi's sarcoma and lymphatic leukemia was recorded in 1931 by Hufnagel and Dupont.<sup>2</sup> Another instance of lymphoblastoma (mycosis fungoides) and hemorrhagic sarcoma of Kaposi was described by Lane and Greenwood<sup>3</sup> in 1933. Our patient was presented before the Manhattan Dermatological Society in 1943, by Dr I. Rosen.<sup>4</sup> The reasons for this report are, first, the small number of reported cases of the coexistence of the two diseases and, second, the unusual pathologic finding of the two diseases in the same lesion.

### REPORT OF CASE

J. K., a Jew, born in Austria, aged 59 years, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Jan. 11, 1943. The patient had an eruption on the left sole and instep and on the inner aspect of the left heel of seven months' duration (fig. 1A). This consisted of irregularly shaped, violaceous plaques 1 to 4 cm in diameter. There were several smaller lesions on the dorsa of the foot and toes (fig. 1B).

In the right cervical and supraclavicular regions, there were enlarged lymph nodes, some discrete and some matted together. There were also large lymph nodes in the axillas and groins.

The patient stated that after roentgen irradiation of the right cervical region the enlargement of the lymph nodes became more pronounced.

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Cole H. M., and Crump, E. S. Report of Two Cases of Idiopathic Hemorrhagic Sarcoma (Kaposi), the First Complicated with Lymphatic Leukemia, *Arch. Dermat. & Syph.* 1: 283 (March) 1920.

2. Hufnagel, L. and Dupont, A. Sarcomatose idiopathique de Kaposi et leucémie lymphoïde, *Bull. Soc. franç. de dermat. et syph.* 38: 656 (April) 1931.

3. Lane C. G., and Greenwood, A. M. Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, *Arch. Dermat. & Syph.* 27: 643 (April) 1933.

4. Rosen I. Idiopathic Hemorrhagic Sarcoma and Lymphatic Leukemia, *Arch. Dermat. & Syph.* 48: 566 (Nov.) 1943.

*Preliminary Laboratory Data*—Examination of the urine showed no abnormalities, and the Wassermann and Kahn reactions were negative.

A complete blood count revealed 3,600,000 erythrocytes, 76 per cent hemoglobin, 13,600 leukocytes, 8 per cent neutrophils and 89 per cent lymphocytes. Approximately 10 per cent were immature cells. Clot retraction was

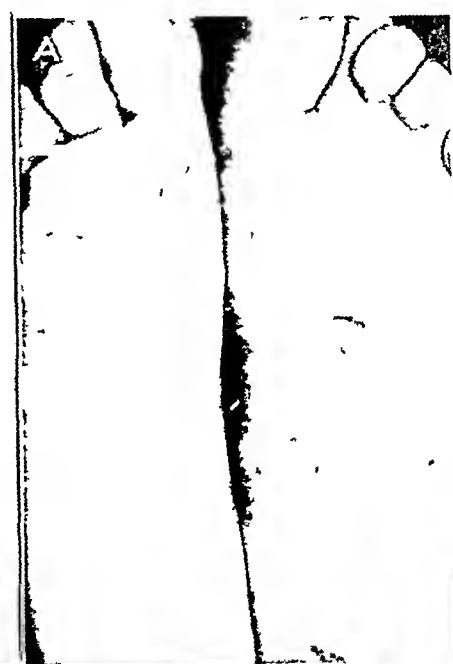


Fig. 1—A, lesion on the sole of the left foot, B, lesions on the dorsum of the foot and toes.

slightly retarded, and the fragility of the erythrocytes was normal.

Tissue taken for biopsy from a small, pea-sized, lesion on the middle of the left sole near the border of the foot revealed the following features (fig. 2).

Throughout the middle and upper portions of the cutis, there were a diffuse mass composed of dilated blood and lymphatic vessels, some increase in connective tissue and a diffuse cellular infiltration. The overlying epidermis



was irregularly acanthotic, the palisade layer intact and the horny and granular layers increased. There were no other important changes within the epidermis.

The blood vessels were dilated, the walls of some were thinned and of others swollen. Some of the vessels were filled with blood elements. There were numerous lymphatic vessels and lymphatic spaces. The cellular elements were small round cells, angioblasts and spindle cells. There was an increase in the connective tissue and a diffuse pigmentation that gave a positive Perles reaction (fig 3).

**Hospital** On admission it was noted that besides Kaposi's sarcoma, the blood count revealed lymphatic leukemia. Also there were generalized enlargement of lymph nodes and a large spleen. Roentgenotherapy had been given until two months prior to his entrance into the hospital, but because of a leukopenia and anemia it was discontinued and transfusions were given. On July 28 a sore throat and fever developed, and they became progressively worse.

The diagnoses were lymphatic leukemia, hemorrhagic sarcoma of the left leg and infected tonsils.

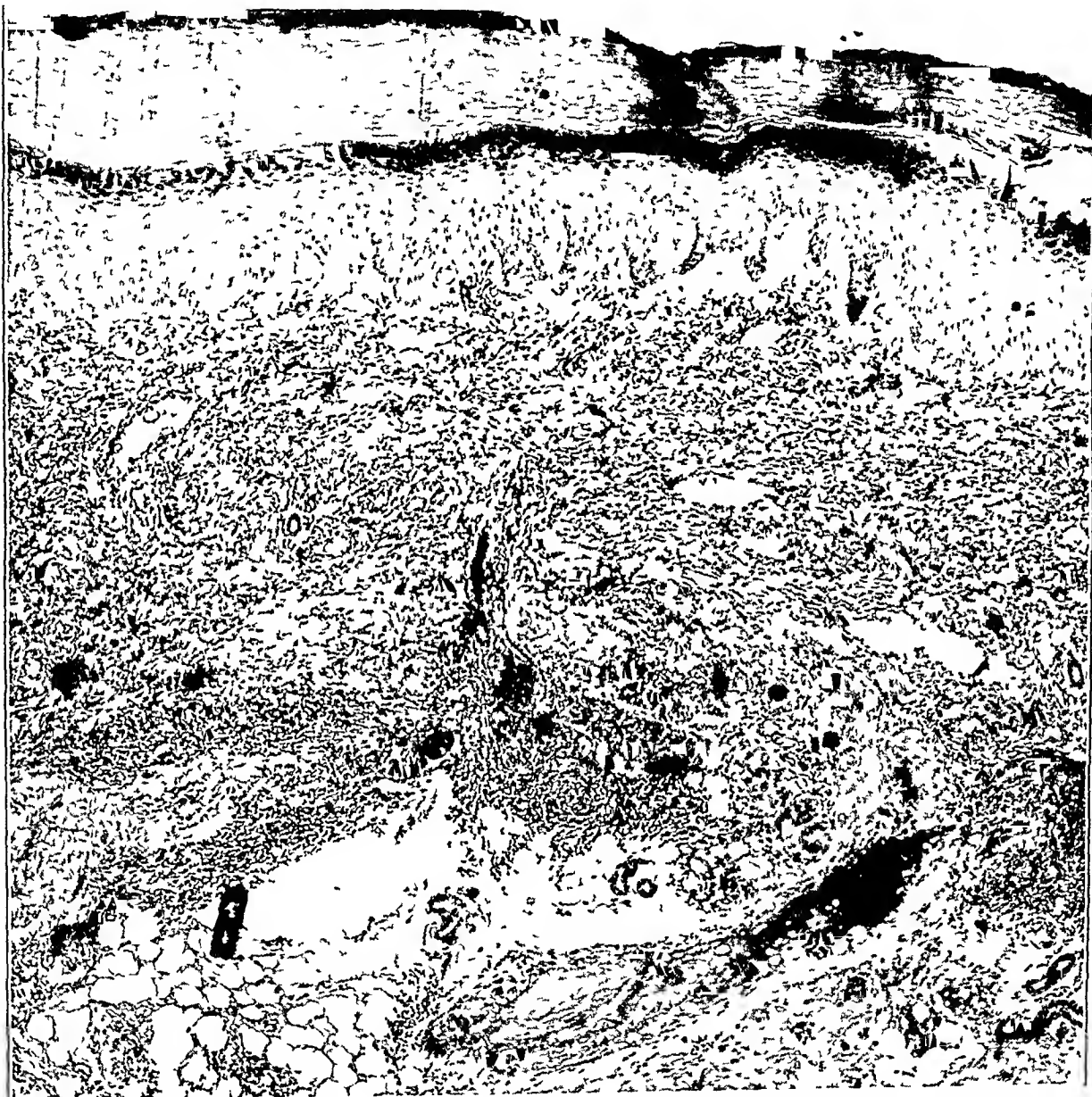


Fig 2—Kaposi's sarcoma in the middle and upper layers of the cutis, lymphatic leukemia in the deep layers of the cutis (low power)

Diagnosis of this part of the section was Kaposi's sarcoma.

In the deep portion of the cutis, at the junction of the fat, the vessels were dilated and there was a tremendous cellular reaction about them. The cells were all uniform in size and shape, having round hyperchromatic nuclei and a narrow rim of faintly staining cytoplasm (fig 4).

Diagnosis of this portion of the section was lymphatic leukemia.

**Hospital Record**—On Aug 1, 1943, the patient was admitted to the Post-Graduate Medical School and

On the morning of August 12, the patient had a temperature of 106, with a cough and pain in the chest on inspiration and rales. The diagnosis was pneumonitis. The patient's condition became steadily worse, and he died the same night.

The final diagnoses were Chronic lymphatic leukemia (aleukemic phase), Vincent's infection of the tonsil, bronchopneumonia, pneumococcus type XXI.

**Laboratory Data**—Bacteriology. Cultures of material from the nose and throat yielded organisms which were predominantly pneumococci. Typing of sputum by the

Neufeld method indicated pneumococci of type XXI  
Cultures of the blood showed heavy growths of hemolytic  
streptococci. Two smears of material from the throat  
were positive for Vincent's organism.  
Vitamin studies revealed the vitamin C level of the  
blood plasma to be 0.2 mg (normal 0.7 to 1.4 mg) per  
hundred cubic centimeters.  
Hematologic studies revealed the sedimentation rate  
at quarter-hour intervals to be 35, 80, 117 and 139 mm,  
the maximum for males being 10 mm an hour.  
A blood count showed 3,600,000 erythrocytes and  
13,600 leukocytes. After considerable therapy with  
filtered and with unfiltered roentgen rays to both the  
lymph nodes and the Kaposi lesions, the count fell on

central thickening, this, together with moderate lymphoid  
nodulation at the hilus, appeared to be of rather long  
standing and is probably somewhat discernible in the  
upper lobe of the right lung.  
Of more recent origin appeared a spotty, more or less  
segmental, pneumonic infiltration extending beyond the  
lower cornu apparently more or less posteriorly toward  
the bases. Continued observation and further compara-  
tive exposures appeared to be advisable.

#### COMMENT

There are some features which Kaposi's sar-  
coma and the lymphoblastomas have in common,

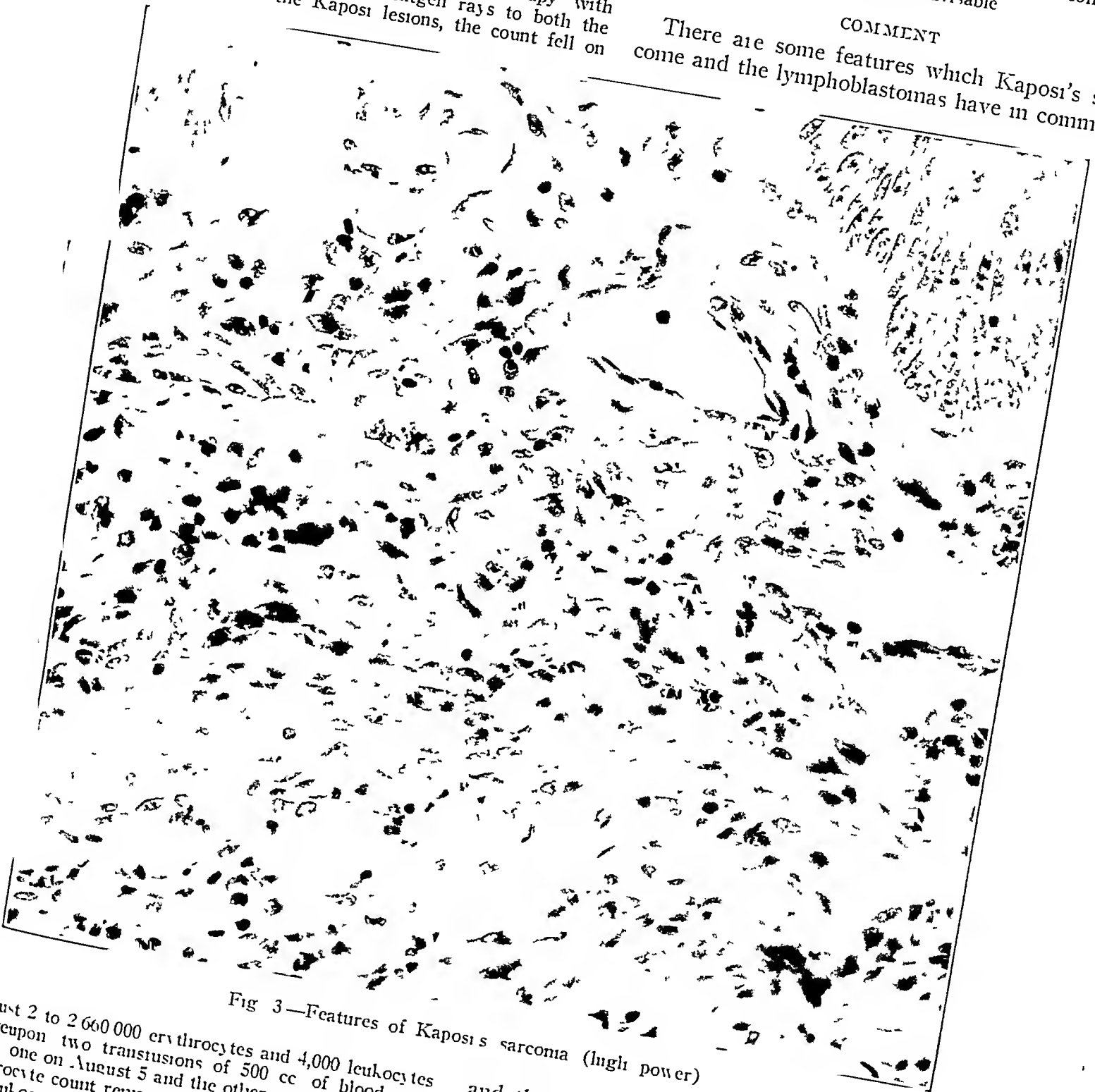


Fig. 3—Features of Kaposi's sarcoma (high power)

August 2 to 2,660,000 erythrocytes and 4,000 leukocytes.  
Thereupon two transfusions of 500 cc. of blood were  
given one on August 5 and the other on August 9. The  
erythrocyte count remained approximately the same, but  
the leukocyte count continued to drop and on August  
12 was 2,350.  
Many examinations of the urine were made, but no  
important abnormalities were noted.  
Roentgenographic examination of the chest on August  
12 revealed a moderate degree of hilus, root branch and

and there are some ways in which they differ.  
The former are chiefly from the clinical aspect,  
while the latter are mainly from the pathologic  
viewpoint. For example, the two diseases are  
similar in that both are radiosensitive and both  
may be present for months and even years. How-  
ever the microscopic observations are unlike,  
for in Kaposi's sarcoma there are angioblasts

(endothelioid) and spindle cells, new blood and lymph vessels, development of fibrous tissue and absence of leukocytes. The lymphoblastomas do not have the first three, but they may have the last.

Kaposi's sarcoma and lymphoblastoma are not uncommon dermatoses, and yet there are few cases of their coexistence in the literature. One would expect this association if it were purely accidental that both diseases occurred in the same patient. While it is assumed that it is just chance,

all 3 patients died of leukemia and not of idiopathic hemorrhagic sarcoma. In the case reported by Lane and Greenwood<sup>3</sup> there was the further complication of mycosis fungoides, yet even in their patient there was evidence of a mild form of lymphatic leukemia. Hufnagel and Dupont suggested that all persons with Kaposi's sarcoma have careful blood examinations. Not only in their case, but in several other cases which they cited a high leukocyte count, up to 37,000, was found. We have been able to check

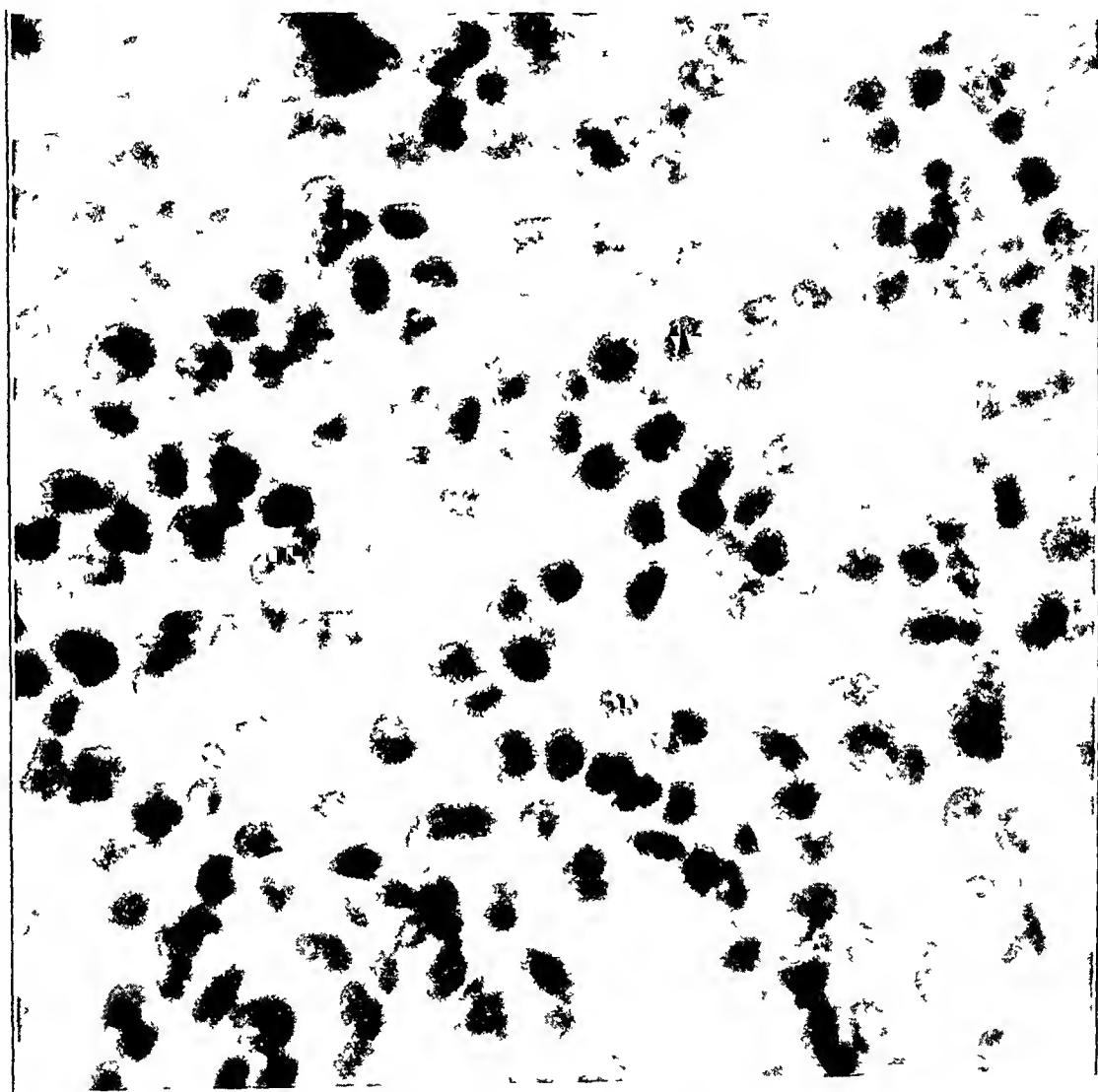


Fig. 4—Cellular infiltration of lymphatic leukemia (high power)

there is no scientific proof at the present to substantiate such a statement. The authors of the reports cited were unable to say what the relationship is, if any. This negative view, we feel, is much safer, for it would be unwise to attempt any conclusions on this point from observations in only 4 cases.

In the cases of Cole and Crump<sup>1</sup> and Hufnagel and Dupont<sup>2</sup> and in ours, the clinical features were those of Kaposi's sarcoma while the hematologic pictures were those of leukemia. Also

on several of our cases of Kaposi's sarcoma, but we have found nothing significant in the hematologic pictures.

However, another point of interest along the same line is the presence of enlarged lymph nodes. Involvement of lymph nodes, except perhaps regional, is not a feature of Kaposi's sarcoma, and in all cases of such involvement there should be further investigation of the possibility of lymphatic leukemia.

In the case under discussion the patient had both Kaposi's sarcoma and lymphatic leukemia in the same lesion, yet each disease was distinctly separate from the other. Kaposi's sarcoma was present in the middle and upper layers of the cutis, and lymphatic leukemia could be seen in the deep part of the cutis. Also, we cannot say which came first and whether or not the presence of the one predisposed to the development of the other. It is not surprising that this may have occurred, for it is common for one dermatosis to develop in the wake of another that is receding and still be unrelated to the other disease. Therefore, even if one did predispose to the development of the other, we believe that this would be no proof of their similarity.

## SUMMARY

A patient was observed with coexisting Kaposi's sarcoma and lymphatic leukemia.

The pathologic picture showed both diseases in the same lesion. This appears to be the first time that such an event has been reported.

Careful hematologic studies should be made in all cases of Kaposi's sarcoma, and enlarged lymph nodes should be investigated, for they are not necessarily a part of the picture of this disease.

The points of similarity between Kaposi's sarcoma and lymphatic leukemia are chiefly clinical, while pathologically the two diseases are considerably different.

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# CUTANEOUS AND ARTICULAR MANIFESTATIONS IN LYMPHOGRANULOMA VENEREUM

ACTIVATION OF THE DISEASE BY THE FREI TEST

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The more familiar manifestations of lymphogranuloma venereum are the result of a chronic, progressive involvement of the genitalia, rectum and associated lymphatic system. The virus may produce disease elsewhere as the result of inoculation in extragenital regions, such as the mouth, hands<sup>1</sup> or upper respiratory tract<sup>2</sup>. There may be an extensive spread from the original sites of involvement, as in the instances of colitis and colonic strictures caused by infection with the virus of this disease<sup>3</sup>. A true metastatic infection may occur, as has been illustrated by isolation of the virus from the spinal fluid of a patient with meningoencephalitis<sup>4</sup>.

Accompanying these localized infections in both the early and the later stages, there may be a variety of generalized constitutional effects and of certain more specific manifestations, as cutaneous eruptions and arthritis<sup>5</sup>. Some, such as fever, headache, vomiting, loss of weight and progressive anemia, are the nonspecific effects of the acute or chronic stages of any infection. Others, as arthritis, cutaneous eruptions, splenomegaly, episcleritis, conjunctivitis and stomatitis, have been regarded by some observers as allergic phenomena and by others as evidences of actual invasion of these regions by the virus.

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1 Bloom, D. Lymphogranuloma Venereum. Present Status, New York State J. Med. **38** 616, 1938.

2 Harrop, G. A., Rake, G. W., and Shaffer, M. F. Group of Laboratory Infections Ascribed to Lymphogranuloma Venereum, Tr. Am. Clin. & Climatol. A. **56** 154, 1941.

3 Paulson, M. Diagnosis of Colitis Associated with Virus of Lymphogranuloma Venereum by Bowel Antigen, Am. J. Digest. Dis. **5** 554, 1938.

4 Sabin, A. B., and Aring, C. D. Meningoencephalitis in Man Caused by Virus of Lymphogranuloma Venereum, J. A. M. A. **120** 1367 (Dec. 26) 1942.

5 (a) Coutts, W. E. Contribution to Knowledge of Lymphogranulomatosis Venerea as General Disease, J. Trop. Med. **39** 13, 1936. (b) Eberhard, T. P. Generalized Lymphogranuloma Inguinale, Ann. Surg. **107** 380, 1938. (c) Gutman, A. B. Systemic Manifestations of Lymphogranuloma Venereum, with Illustrative Case Reports, New York State J. Med. **39** 1420, 1939. (d) Bloom<sup>1</sup>.

of lymphogranuloma venereum. The occasional preparation of an active Frei antigen from joint fluid<sup>6a</sup> or from cutaneous lesions<sup>6</sup> suggests the presence of the virus, but in contrast there have been reports of failure to obtain an active Frei antigen from cutaneous lesions<sup>7</sup> and from joint fluids<sup>8</sup>. Failure of attempts to isolate the virus from joint effusions by inoculations of laboratory animals has also been reported<sup>8</sup>.

The articular manifestations of lymphogranuloma venereum described by different observers appear for the most part to have fallen into one of three general clinical categories:

1 Arthralgia. Migratory pains in the joints usually fleeting, without objective evidence of articular disease are of common occurrence in the early weeks of the infection<sup>9</sup>. They also appear in the chronic stages, when they may be more persistent. Koehnlich<sup>10c</sup> noted this symptom in 3 per cent of 375 patients, more often among those with chronic rectal lesions. In his experience, the knee was most frequently involved. Levy, Holder and Bullowa<sup>10</sup> estimated

6 (a) Kleeberg, L. Lymphogranuloma inguinale mit Erythema nodosum und aphthosen Erscheinungen am Genitale, Dermat. Wchnschr. **91** 1376, 1930, cited by Saenz<sup>7b</sup>. (b) Midana, A. Lesioni cutanee nell'infogranulomatosi inguinale acuta di Nicolas e Favre, Giorn. ital. di dermat. e sif. **75** 1743, 1934, cited by Goldberg and Fonde<sup>7a</sup>. (c) Nicolau, S. Lesions cutanees lymphogranulomateuses chez une femme atteinte du syndrome elephantiasique vulvo-ano-rectal, Ann. de dermat. et syph. **5** 1, 1934, cited by Goldberg and Fonde<sup>7a</sup>.

7 (a) Goldberg, L. C., and Fonde, G. H. Recurrent "Lymphogranulomatid" (?) Reactions in Course of Lymphogranuloma Venereum, Proc. Soc. Exper. Biol. & Med. **45** 259, 1940. (b) Saenz, B. Unusual Form of Allergic Cutaneous Reaction in Lymphogranulomatosis Inguinalis. Report of Case, Arch. Dermat. & Syph. **31** 348 (March) 1935.

8 (a) Chapman, E. M., and Hayden, E. P. Lymphogranuloma Inguinale. Clinical Study of Thirty Cases of Sixth Venereal Disease in Natives of New England, New England J. Med. **217** 45, 1937. (b) Gutman<sup>5c</sup>.

9 Frei, W. Venereal Lymphogranuloma, J. A. M. A. **110** 1653 (May 14) 1938. Bloom<sup>1</sup>. Coutts<sup>5a</sup>. Eberhard<sup>5b</sup>. Gutman<sup>5c</sup>.

10 Levy, J. G., Holder, E. C., and Bullowa, J. G. M. Stricture of Rectum Due to Lymphogranuloma Venereum. Symptoms and Treatment with Sodium Sulfanil Sulfamate, Am. J. Digest. Dis. **9** 237, 1942.

its occurrence in chronic cases at 5 per cent. It may also be evoked by the intradermal Frei test<sup>11</sup> and may appear in the course of reactions to the intravenous administration of Frei antigen for therapeutic purposes.<sup>12</sup>

2 Acute polyarthritis Painful swelling of the joints with redness and increased temperature of the overlying skin may accompany the early or later stages of the disease.<sup>13</sup> Coutts<sup>5a</sup> reported the appearance of an effusion in 3 such patients, and from one of the effusions an active Frei antigen was prepared. Gutman<sup>5c</sup> found that the ankles, hips, elbows and wrists were most frequently involved by this type of arthritis. It seems to disappear rapidly without residual impairment of joint function. Chapman and Hayden<sup>8a</sup> described a case in which an acute migratory arthritis, together with erythema nodosum, was apparently evoked by a Frei test. Acute articular involvement of this nature is apt to be accompanied with a constitutional reaction, with fever and malaise.

3 Chronic, recurrent polyarthritis with effusion In the later stages of the disease, there may be recurrent episodes of effusion into one or more joints.<sup>14</sup> These do not appear to result in deformity or permanent impairment of function of the joint. Attempts to isolate the virus by inoculations in animals or to make a potent Frei antigen from joint fluid have been unsuccessful.<sup>15</sup> Such an effusion has been reported following the intradermal Frei test.<sup>8a</sup> Joint involvement of this sort in contrast to that just described, tends to be unaccompanied by a pronounced constitutional reaction and does not exhibit much evidence of acute inflammation.

A wide variety of cutaneous lesions have been described as occurring in the course of lymphogranuloma venereum. Coutts has pointed out that these may be grouped as (a) generalized and (b) limited to the region especially affected by the virus. In the latter group belong the ulcerative disorders classified by Wien and Perlstein<sup>16</sup> as (a) simple ulceration of the skin, (b) ulceration secondary to involvement of lymph

nodes and (c) ulceration developing on an esthiomene.

The generalized cutaneous lesions are said to fall for the most part into the classification of either erythema nodosum or erythema multiforme.<sup>17</sup> They may occur early or late in the disease and appear sometimes to be evoked by such procedures as administration of Frei antigen,<sup>18</sup> roentgen ray therapy<sup>7b</sup> or incision of buboes.<sup>7a</sup> In some instances, these generalized eruptions have been ascribed to the presence of the virus in the lesions. This belief has been supported in individual cases by the preparation of an active Frei antigen from tissue extracted from such lesions as an ecthymiform pyodermitis over the abdomen, thighs and buttocks<sup>6b</sup> and indurated plaques on the vulva and buttocks<sup>6c</sup> and from the fluid of bullae.<sup>6a</sup> Failure to obtain a potent Frei antigen from tissue extracts of cutaneous lesions has been reported in instances of generalized vesiculopustular and papular eruptions.<sup>7</sup> Benedek and Olkon<sup>17a</sup> have reported demonstration of Miyagawa's elementary bodies by special stains in a patient with papulopustular lesions.

The generalized eruptions have been interpreted by other observers as the expression of a cutaneous allergy to the virus or to the products of infection with it. Hellerstrom<sup>19</sup> has studied the occurrence of erythema nodosum during the course of lymphogranuloma venereum, both spontaneous and after the intracutaneous or intravenous administration of the Frei antigen. He concluded that the eruption is the manifestation and result of an allergic reaction on the part of the skin against the micro-organisms and probably also against their allergens, which reach the skin by the hematogenous route from the primary focus. Saenz<sup>7b</sup> also concluded that the lesions of his patient had an allergic cause.

Whether these cutaneous and articular manifestations are to be regarded as resulting from actual infection in these regions with the virus of lymphogranuloma venereum or as allergic phenomena, it appears that many of them which occur spontaneously during the course of the disease may also be evoked on occasion by the administration of Frei antigen. This material

11 Coutts<sup>5a</sup> Chapman and Hayden<sup>8</sup>

12 Kornblith, B. A. Lymphogranuloma Venereum. Treatment of Three Hundred Cases with Special Reference to the Use of Frei Antigen Intravenously, *Am J M Sc* **198** 231, 1939

13 Coutts<sup>5a</sup> Gutman<sup>5c</sup>

14 (a) Frauchiger, E. Polyarthritis Lymphogranulomatosa Inguinalis Tarda, *Schweiz med Wchnschr* **63** 1207, 1933 (b) Gutman<sup>5c</sup>

15 Gutman<sup>5c</sup> Chapman and Hayden<sup>8</sup>

16 Wien, M. S., and Perlstein, M. O. Ulcerative Lesions of Skin in Lymphogranuloma Inguinale. *J A M A* **108** 27 (Jan 2) 1937

17 (a) Benedek, T., and Olkon, D. B. Lymphogranuloma Venereum as Systemic Disease. Report of Case with Involvement of Skin and Eye, *Am J Syph, Gonorr & Ven Dis* **25** 28, 1941 (b) Coutts<sup>5a</sup> (c) Saenz<sup>7b</sup>

18 Lehman, C. F., and Pipkin, J. L. Lymphopathia Venerea with Lichenoid Rash, *Arch Dermat & Syph* **31**-581 (April) 1935 Chapman and Hayden<sup>8</sup>

19 Hellerstrom, S. Das Erythema nodosum-Problem im Lichte des Lymphogranuloma inguinale, *Acta med Scandinav* **109**.1, 1941



has been widely used for therapeutic purposes, most commonly by the intravenous route.<sup>20</sup> The first one or two injections are usually productive of systemic and local reactions of variable intensity. On the basis of experience with 207 patients, Kornblith<sup>12</sup> has listed these as chill, fever (temperature as high as 106 F), malaise, occipital headaches, nausea and vomiting, infrequently a generalized maculoerythematous rash which fades in forty-eight hours, in some cases pains in the joints and occasionally enlargement of buboes and rupture of inguinal abscesses. In a small percentage of cases, some symptoms persisted for as long as five days. He observed no untoward, alarming results of this therapy in any case. The possibility of a more prolonged and disabling reaction to the Frei antigen is illustrated by the patient of Chapman and Hayden in whom erythema nodosum and painful, swollen joints at the wrists, ankles and knees developed three days after the intradermal diagnostic test was given. These symptoms persisted for three weeks, accompanied with an irregular fever with temperatures up to 103 F. Because of the possibility of generalized or focal reactions Frei has warned against the use of the intradermal test "in peracute stages of the disease or in cases in which suppuration occurs near the peritoneum."

The histories of 4 patients with chronic lymphogranuloma venereum are presented with three purposes in mind: (a) to record further examples of the articular manifestations which have been observed in association with lymphogranuloma venereum and to describe the occurrence of tenosynovitis and bursitis in this disease, (b) to describe a type of eruption which has been observed both as a spontaneous phenomenon and as an apparent response to the intradermal Frei test and (c) to illustrate the occurrence of severe, undesirable reactions to the diagnostic Frei test.

#### REPORT OF CASES

CASE 1—W. R., a 25 year old single Negro woman, abruptly, three weeks before her admission to the hospital, experienced a painful swelling of the right ankle, associated with malaise and chilly sensations. One week later the left ankle and right elbow and wrist were similarly affected. Five days before her admission to the hospital, tenderness and pain on motion appeared in the upper lumbar region of the spine. At about the same time she began to note the development of small painless pustules on minor abrasions of the skin.

20 Wien, M. S., and Perlstein, M. O. Intradermal Treatment of Lymphogranuloma Inguinale, *Brit J Dermat* 49 63, 1937. Hellerstrom, S. Injections intraveineuses avec l'antigene de la lymphogranuloma inguinale, *Acta dermat-venereol* 17 293, 1936. Kornblith<sup>12</sup>

Three years before, there had been an indolent, apparently ulcerative lesion of the introitus, which the patient could not accurately describe.

The temperature was 101 F. There were numerous small pustules over the legs, the arms and the face. These were yellow, tense, 2 to 4 mm in diameter and superficial, with only slight erythema and induration around the base. There were warm, tender swellings over the right wrist and elbow, both ankles and the dorsum of the third right toe. These gave the impression of being periarticular. There was a superficial, tender, swollen fluctuant area anterior and inferior to the left lateral malleolus. There was tenderness over the upper lumbar vertebrae. Pelvic examination showed hypertrophy and edema of the labia and an old, healed ulceration of the fourchet and the vaginal orifice. There were several shallow erosions, 5 mm in diameter, with a clean base, over the mucous membrane of the vulva. The cervix appeared normal. There was no adnexal tenderness or induration. Rectal and sigmoidoscopic examination showed no abnormalities, except a few external tags. The results of the remainder of the physical examination proved normal.

The Frei test with chick embryo antigen (lygranum) elicited a strongly positive reaction, an indurated area 12 cm in diameter forming after forty-eight hours and developing after several days into a pustule 4 mm in diameter which ruptured to form an ulcer. The Kahn tests and tests with smears gave negative results. Culture of materials from the cervix showed no gonococci. No spirochetes were found on dark field examination of the vulvar lesions. Erythrocytes numbered 3,700,000 per cubic millimeter, and white blood cells 12,000, with 72 per cent neutrophils, 22 per cent lymphocytes, 1 per cent monocytes and 4 per cent eosinophils. The hemoglobin content was 67 Gm per hundred cubic centimeters, and the serum protein level was 7 Gm. There was an infection of the urinary tract with *Escherichia coli*. Culture of materials from the throat showed a moderate number of beta hemolytic streptococci. Culture of the blood yielded no growth. The spinal fluid was normal. Electrocardiograms showed no evidence of myocardial disease, and roentgenograms of the chest and left knee revealed no pathologic change.

Sixty cubic centimeters of pale, viscid fluid was aspirated from the left knee joint. It contained 70 white cells, with 44 per cent polymorphonuclear leukocytes and 56 per cent large and small mononuclear leukocytes, and was sterile on culture. Culture of pus from the cutaneous lesions yielded no growth. A Frei antigen made from this material elicited no reaction in persons who reacted positively to chick embryo antigen.

The temperature fell to normal during the first week. There was no constitutional reaction to the Frei test. Pain and swelling over the originally affected joints cleared completely in the first five days, leaving no residua. On the fourth day fluid appeared in the left knee joint. The joint was swollen and fluctuant, but not warm, and was only slightly tender. This swelling subsided during the next six days, leaving the joint apparently normal.

During the first seven days pustules continued to appear, principally on the legs. These reached their full development within one or two days and ruptured three to four days later, leaving shallow, clean erosions which healed readily. On the fourth day a chain of pustules appeared along the course of a superficial scratch on the left shoulder. Before her admission

o the hospital, the patient had applied an adhesive plaster across the trunk. This was removed on the first day in the hospital, but by the fifth day approximately fifty pustules had developed over the previous site of the plaster. A subsequent test application of adhesive plaster to the back produced no cutaneous reaction. By the seventeenth day the erosions of the vulva had cleared completely. On the seventh day an area of episcleritis developed on the lateral aspect of the right eye. Ten days later this had subsided completely. The patient was discharged without complaints on the nineteenth day.

*Comment*—This patient, with evidence of chronic lymphogranuloma venereum, exhibited the spontaneous development of acute migratory arthritis or peri-arthritis. There was a definite tenosynovitis with effusion over the left ankle. During the period of observation an effusion appeared in the left knee joint, with little local evidence of acute inflammation and no systemic reaction. These articular manifestations cleared rapidly, without residua. A generalized pustular eruption developed spontaneously. It is noteworthy that this eruption, as did that in 2 of the patients to be discussed, showed a definite tendency to form at the site of spontaneous injuries.

CASE 2—E. L. L., a 32 year old multiparous Negro housewife, had been in good health until four years before her admission to the hospital, when she began to have constipation, with the passage of stools of small caliber, often streaked with blood and mucus, followed by tenesmus. These symptoms gradually became more pronounced. Three years before her admission, after a sprain, a painful swelling of the left ankle developed. This was followed in a week by swelling of the right ankle and during the next four months by migratory involvement of the toes, knees, hips, fingers, wrists, elbows, shoulders and neck. Swelling in a joint appeared rapidly, often overnight, and subsided in one to two weeks. Affected joints were painful on motion but were not red or unusually warm, and she had no associated constitutional symptoms. There was no residual impairment of articular function. During the next three years there were frequent recurring attacks, involving principally the wrists and ankles, always following the same pattern. Two years before her admission her Kahn reaction was found to be positive, and she was given antisyphilitic treatment for a year, but without any obvious benefit. Two months before she entered the hospital she began to have migratory swelling of the wrists, ankles and fingers without intervals between the attacks. This episode, unlike the others, was associated with malaise and weakness.

The temperature was 100 F. Anterior to the lateral malleolus of the right ankle was a tender fluctuant area without redness or increased warmth. This was said to be subsiding. Elsewhere there was no deformity of joints or impairment of motion. Pelvic examination revealed nothing abnormal except a thin, white discharge from the cervix and tenderness over the rectum. There were large hemorrhoidal tabs. The rectal mucosa was firm and granular, and there was tenderness on pressure in all directions. Sigmoidoscopic examination showed diffuse reddening of the rectal mucosa with many fine papular projections but no ulcers. The mucosa bled easily on manipulation. The upper part of the rectum and lower part of the sigmoid appeared entirely normal. There was no stricture. The remainder of the results of the physical examination are not remarkable.

The reaction to the Frei test with chick embryo antigen (lygranum) was strongly positive, eventually forming a pustule 4 mm in diameter in the center of a papule 1 cm in diameter. The complement fixation test for lymphogranuloma elicited a strongly positive reaction in a 1:20 dilution. The Kahn reaction was negative. Erythrocytes numbered 3,600,000 and white blood cells 9,500, with 57 per cent neutrophils, 38 per cent lymphocytes, 2 per cent monocytes, 2 per cent eosinophils and 1 per cent basophils. The hemoglobin content was 7 Gm per hundred cubic centimeters. The stool showed signs of blood with the guaiac test and contained innumerable pus cells. The serum protein was 7.8 Gm per hundred cubic centimeters, the reaction to the "formol-gel" test was positive. A smear of secretions from the cervix showed no gonococci. Culture of materials from the throat grew no beta hemolytic streptococci. Fluid from the fluctuant area over the ankle was pale yellow and contained 5,000 white cells, with 90 per cent mononuclear leukocytes. Fluid from the left knee was pale yellow and viscid and contained 4,600 white cells, with 86 per cent polymorphonuclear leukocytes. Both fluids were sterile on culture. The spinal fluid was normal. An electrocardiogram showed no evidence of myocardial disease. Roentgenograms of the chest and right ankle showed no pathologic changes.

There was no constitutional reaction to the Frei test. Twelve hours after it was given, both knees became slightly painful, and by the following day there were obvious signs of fluid in each. They were painful on motion but not red or warm. In approximately ten days they had returned to normal. During the first twelve days, the temperature fluctuated between 99 and 102 F, slowly falling to a normal value.

*Comment*—This patient, with chronic proctitis, had a three year history of recurrent, migratory swellings of the joints, with little or no constitutional reaction and without residual impairment of articular function. On her admission there was a subsiding tenosynovitis, with effusion, over the right ankle. During the period of observation, an effusion developed in both knee joints, with little local evidence of acute inflammation and with no constitutional reaction.

CASE 3—E. L., a 25 year old single Negro woman,<sup>21</sup> was well until seven months before her admission to the hospital, when there was a gradual development of constipation. Stools become small in caliber. Bowel movements were preceded by a gush of watery, red material, followed by free bleeding and tenesmus. Seven months before her admission there was transient tenderness over the right achilles tendon. Four months later a painful, tender, warm swelling developed over the anterior surface of the right knee, which lasted a week. Four days before admission the left knee became similarly affected, and tenderness appeared over the left achilles tendon and over the medial aspect of the right patella.

The temperature was 99.8 F. Over the lateral anterior aspect of the left knee there was a swollen, warm, exquisitely tender area 4 cm in diameter. There were similar areas 1 cm in diameter on the right patella and on the left achilles tendon. There was an area of episcleritis in the left eye. Over the cardiac apex there was a soft systolic murmur. Pelvic examination revealed nothing abnormal except a slight, white cervical discharge. The rectum was non-tender on examination, and sigmoidoscopic examination

21 This patient was observed at the Peter Bent Brigham Hospital, Boston.

showed that the rectal mucosa was granular and diffusely injected, with many small bleeding points and occasional flecks of yellow exudate. At about 15 cm from the anus, areas of normal mucosa began to appear. The remainder of the physical examination disclosed no abnormalities.

The reaction to the Frei test with chick embryo antigen was strongly positive. A central pustule developed, which ruptured eventually and formed an ulcer, 1 cm in diameter, on an indurated base approximately 3 cm in diameter. The Hinton and Wassermann reactions were negative. Erythrocytes numbered 3,700,000 and white blood cells 10,000, with 76 per cent neutrophils, 18 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The hemoglobin content was 6 Gm per hundred cubic centimeters. Stools showed innumerable red cells and white cells but no amebas or cysts. The serum protein was 8.4 Gm per hundred cubic centimeters, with 4.7 Gm of globulin. Culture of materials from the cervix showed no gonococci. No beta hemolytic streptococci were grown on culture of materials from the throat. Cultures of the stool were negative for enteric pathogens. Cultures of the blood showed no growth. Materials aspirated from pustules and from areas of tenosynovitis were sterile on culture. Results of the Widal test and the agglutination tests for *Bacillus paratyphosus* B, *Salmonella supestifer* and *Brucella abortus* were negative. The virus of lymphogranuloma venereum could not be recovered by inoculation of white mice and guinea pigs with materials from pustules and from areas of tenosynovitis or with stools or blood.

Several hours after the Frei test was administered, the temperature rose to 102 F, and by the third day had reached 105 F. It was spiking in character but had a gradual rise to a mean of 103.5 F by the fourteenth day. Thereafter, it declined to an average of 100 F. On the third day superficial pustules, 2 to 4 mm in diameter, began to appear over the face, arms and trunk. They ruptured to form shallow ulcers and by the eighth day were all regressing. On the tenth day a second crop of pustules appeared in the same regions and on the buttocks. They showed a definite tendency to form at the site of needle punctures. A satellite ring of pustules appeared at the margin of the reaction to the Frei test. By the fifteenth day these were healing. The original areas of periarticular inflammation cleared within five to six days. Fresh outbreaks of tenosynovitis occurred on the fourth day over the right great toe and on the eleventh day over the third left toe. During the second week there was a hacking, paroxysmal cough, productive of small amounts of rusty sputum, associated with generalized wheezes through both lung fields. Culture of the sputum yielded no predominant organisms, and repeated roentgenograms of the chest revealed nothing abnormal. Bowel movements had been frequent throughout this time, but by the twenty-fourth day the patient began to have an almost continuous discharge of blood, pus and mucus. Sigmoidoscopic examination revealed numerous shallow ulcers. There were abdominal pain and distention and wasting. On the fiftieth day a transverse colostomy was performed, proximal to the apparent limit of involvement of the colon. Thereafter there was a slow gain of weight and strength, and the patient was discharged to be kept under observation.

*Comment*—This patient, with chronic proctitis, had recurrent attacks of acute tenosynovitis and, apparently, bursitis, with local evidence of acute inflammation. There was a prolonged febrile reaction to the Frei test, with

the appearance of a generalized eruption similar to that in case 1. A severe bronchitis developed. There was an exacerbation and extension of the preexisting chronic proctitis, with the eventual development of acute, ulcerative colitis.

**CASE 4**—A J., a 35 year old Negro woman, was found to have a positive Kahn reaction one year before her admission to the hospital and was given antisyphilitic therapy. After she had had a prolonged course of treatment with bismuth, stomatitis developed six weeks before her admission. This improved only slowly under treatment and was associated with weakness and malaise. Eight days before her admission she began to have pain and tenderness in the right flank, unaccompanied by symptoms referable to the urinary tract. With this complaint she was admitted to the hospital. Eight years before, she had had a vaginal discharge and severe bilateral pain in the lower part of the abdomen. For several years she had required frequent laxatives.

The temperature was 100.6 F. Over the forehead and malar eminences there were several papular lesions, 5 mm in diameter, with a small central vesicle having a minute umbilication. There were a few reddened nodules on both palms. The gums were swollen and inflamed and demonstrated a bismuth line. There was a moderate, firm, nontender enlargement of lymph nodes along both posterior cervical chains and in the left axilla. A soft systolic murmur was heard at the cardiac apex. There was tenderness in the right costovertebral angle and in the right flank. Pelvic examination showed tenderness and induration in both fornices. There were several hemorrhoidal tabs. A firm, tender rectal stricture, which easily admitted the finger, was palpated 6 cm beyond the external sphincter.

The reaction to the Frei test with chick embryo antigen was strongly positive, forming a papule 1.5 cm in diameter, with a central pustule which ruptured to form a large, draining ulcer. The Kahn reaction was negative. The urine contained a few pus cells, but culture showed no organisms. Tests of renal function and a roentgenogram of the region of the kidneys showed no abnormalities. Erythrocytes numbered 4,200,000 and white blood cells 8,700, with 45 per cent neutrophils, 50 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils. The hemoglobin content was 10.8 Gm per hundred cubic centimeters. Examination of the stool showed innumerable red and white blood cells. The serum protein was 10.1 Gm per hundred cubic centimeters. The complement fixation test for gonococci gave a negative result. Cultures of the blood yielded no growth. Roentgenologic study after a barium sulfate enema showed a rectal stricture and an irregular mucosal pattern of the transverse and descending colon. A roentgenogram of the chest showed nothing abnormal. The spinal fluid was within normal limits.

A few hours after the Frei test was administered, the temperature rose to 102.6 F and the patient complained of generalized malaise. For the next four days the temperature varied between 100 F and 104 F. Thereafter, it fell gradually to normal. The tenderness of the right flank subsided during the first two to three days.

Several hours after the Frei test was given, the patient began to complain of painful stiffness of the right wrist. This had subsided by the following day, but there was pain and soreness in the finger tips. On the same day a tender, warm, reddened area, approximately 5 cm in diameter, appeared over the medial border of the left foot. This disappeared during the next two days. On the thirtieth day the left knee became swollen, fluctuant and moderately tender but not warm. The swelling subsided completely in the next two days.

On the day after the Frei test, the lesions on the face began to come out more thickly and appeared also over

the right forearm, the site of the test. In those on the palms there also developed a small central vesicle with a minute umbilication. They were relatively deep seated. By the seventh day these lesions began to subside slowly, clearing on approximately the thirteenth day. On the seventh day superficial pustules, 2 to 4 mm diameter, began to appear on the buttocks, sparsely over the back and chest and occasionally at the site of needle punctures. They ruptured in a few days to form ulcers, which appeared to become secondarily infected on the buttocks. By the thirty-third day the cutaneous lesions had healed completely, and the patient was discharged.

*Comment*—This patient, with chronic proctitis and a rectal stricture, exhibited two types of cutaneous lesions. The first consisted of erythematous papules with a small vesicle having a minute umbilication and resembled that described by Saenz and by Goldberg and Fonde. The second appeared during the course of a severe febrile reaction to the Frei test, and the lesions were identical with those occurring in cases 1 and 2. The recurrence of this eruption and the secondary infection of the resultant ulcers on the buttocks considerably prolonged the patient's stay in the hospital. The febrile reaction to the Frei test was accompanied in its early stages by arthralgias and by a transient tenosynovitis on the left foot. During the period of observation there was a fleeting effusion into the left knee, without decided local or constitutional reaction.

#### COMMENT

The varieties of multiple involvements of the joints hitherto described in the course of lymphogranuloma venereum can be classified as arthralgias, acute polyarthritis and chronic recurrent arthritis with effusion. Cases 1, 2 and 4 illustrate at least two of these varieties. In case 4 the patient had fleeting articular pains which appeared during the first forty-eight hours after the Frei test. The patient in case 2 had a three year history of recurrent migratory articular swelling, subsiding in one to two weeks. While he was under observation, effusion of both knee joints developed, with minimal local inflammation and without a constitutional reaction. In cases 1 and 4, the patients exhibited similar effusions into the knee while under observation. There were moderate tenderness and pain on motion but no increased heat or redness of the overlying skin. The fluid from 2 patients was examined. It was pale and viscid containing in one instance 4600 white cells per cubic millimeter, with a predominance of polymorphonuclear leukocytes and in the other 700 white cells, with an equal distribution between polymorphonuclear and mononuclear leukocytes. These fluids were sterile. In each patient the effusion appeared develop fully within the first twenty-four hours. It subsided within three to ten days leaving no impairment of joint motion. Roentgen examination of affected joints in 2 patients showed no bony abnormalities. In case 2 it could not be determined whether the warm, tender swelling over several joints already sub-

siding on the patient's admission to the hospital, represented primarily an acute arthritis or an inflammation of the periarticular tissues.

In cases 1 and 2 a definite, though apparently subsiding, tenosynovitis was present on the lateral inferior aspect of the ankles of the patients. Fluid from one of these areas contained 5000 white cells per cubic millimeter, 90 per cent of which were mononuclear leukocytes. The fluid was sterile. In case 3 acute tenosynovitis over the achilles tendon and the dorsum of the toes was observed. Fluid aspirated from one of these lesions was sterile on culture. Attempts to demonstrate the presence of the virus by animal inoculation were unsuccessful. This was also true of fluid aspirated from one of the subcutaneous areas of acute inflammation over the patellas. These lesions were regarded as examples of bursitis. All such lesions subsided completely within one to two weeks after their appearance. No previous reports have been found of the occurrence of tenosynovitis or bursitis in the course of lymphogranuloma venereum, with the possible exception of Frauchiger's<sup>14a</sup> (case 2), in which a sterile, periarticular abscess developed over the region of the right wrist.

It is recognized that inflammatory disorders of joints and synovial membranes in patients with lymphogranuloma venereum may not be related directly to the disease but may instead be the result of secondary bacterial infection in the regions primarily involved by the virus. In this connection it may be significant that articular manifestations are most common in patients with chronic proctitis. In addition, the possibility of other disease entities cannot be excluded. Some, if not all, of these patients must have had a gonococcic infection in the past. Negative results of smears and cultures of materials from the cervix, of complement fixation tests for gonorrhea and of cultures of joint fluid do not exclude the diagnosis of gonococcic arthritis. As an illustration of further possibilities, it was found that 1 patient in this series harbored beta hemolytic streptococci in the pharynx, suggesting at first the possibility of acute rheumatic fever. However, in a general way, the disorders of the joints of these patients distinguish themselves from the more common varieties of inflammatory disease of the joints by a combination of rapidity of development and regression, frequency of effusion with relatively mild signs of inflammation, rapid recovery of normal function and normal appearance of the joint on roentgen examination. In the absence of more direct proof it is only the accumulation of case reports which will clarify the situation.

The pustular eruption which appeared in 3 of these patients with chronic lymphogranuloma venereum has not been commonly observed. In 1 patient it occurred spontaneously in the course of an acute polyarthritis or peri-arthritis. In the other 2 patients, it broke out two to five days after the administration of the Frei test, during the resultant febrile reaction. In all patients it was associated with fever and arthritis or tenosynovitis. No patient gave a history of previous eruption, and there had been no medication known to be capable of producing such lesions. The pustules appeared over face, trunk and extremities, except in case 4, in which the face of the patient was spared of pustules but was the site of a different (previous) eruption. The outbreaks tended to come in crops, and individual lesions reached their full development in one to two days. The pustules were superficial, yellow and tense and ordinarily measured 2 to 4 mm in diameter. They produced relatively no reaction, with only a narrow zone of erythema and induration about the base. Three to four days after reaching full development they ruptured, leaving a shallow erosion with a clean base. These erosions healed readily, usually without any scar formation, except in case 4, in which the lesions on the patient's buttocks became secondarily infected. Related lesions of the mucous membrane were not observed, except possibly in case 1 in which the patient had numerous shallow erosions on the labia minora at the time of the generalized eruption. These healed readily, together with the cutaneous lesions. In all 3 patients there was a distinct tendency to the development of typical pustules on the site of superficial scratches and needle punctures. The pustular fluid was sterile on culture in all instances. A Frei antigen made from this material in case 1 gave negative results in tests on patients known to have a positive reaction to chick embryo antigen (lygranum). In case 3, the intracranial inoculation of white mice with pustular fluid failed to produce disease in the animals.

It is believed that the intradermal Frei test with chick embryo antigen produced distinctly harmful results in 2 patients. In case 3 the patient suffered a prolonged febrile reaction of at least fourteen days, with the appearance of a pustular eruption forty-eight hours after the test. During the second week there was a severe bronchitis with an irritating, paroxysmal cough, but the relation of this to the remainder of the reaction is not clear. Approximately three weeks after the test while the rest of the manifestations were subsiding, there was an exacerbation and

extension of the preexisting chronic proctitis, with the eventual development of ulcerative colitis. This required the performance of a colostomy. In case 4 the patient had a severe febrile reaction of five days' duration with fleeting arthralgias and tenosynovitis. This was followed by the appearance of several successive crops of superficial pustules. Those over the buttocks, where the eruption was thickest, became secondarily infected, and the required treatment of these lesions greatly prolonged the stay in the hospital. There was no exacerbation of the preexisting chronic proctitis in this patient.

The chick embryo antigen (lygranum)<sup>22</sup> which was used for intradermal testing of these patients is a consistently potent antigenic preparation made from virus cultured on the yolk sac of the developing chick embryo. It is an invaluable diagnostic aid in regions where lymphogranuloma venereum is a prevalent disease. Because of the possibility of violent generalized reactions, with exacerbation of the disease process as well as development of local ulceration at the site of the test, it is suggested that this material be diluted for use for patients who appear to be in active stages of the disease.

#### SUMMARY

A study of the literature dealing with polyarthritis and cutaneous eruptions in the course of lymphogranuloma venereum showed that reported articular manifestations have been principally arthralgias, acute polyarthritis and chronic recurrent arthritis with effusion. A wide variety of cutaneous lesions have been reported, the majority of which have taken the form of erythema nodosum or erythema multiforme.

In the 4 cases I observed that the articular manifestations resembled those described by other authors, except for the additional appearance of acute tenosynovitis and bursitis with effusion. All forms of involvement subsided rapidly without residua. A generalized pustular eruption occurred in 3 patients. In 1 patient it occurred spontaneously, in the other 2 it was thought to be evoked by the intradermal Frei test with chick embryo antigen (lygranum). Two patients had severe reactions to the Frei test, with an exacerbation of certain of the manifestations of lymphogranuloma venereum.

It is suggested that the preparation of chick embryo antigen be diluted for use for patients whose disease appears to be in an active stage.

<sup>22</sup> Grace, A. W., Rake, G., and Shaffer, M. F. New Material (Lygranum) for Performance of Frei Test for Lymphogranuloma Venereum, *Proc Soc Exper Biol & Med* 45: 259, 1940.



# CUTANEOUS DIPHTHERIA AS A MILITARY PROBLEM

REVIEW OF THE LITERATURE, WITH REPORT OF A CASE

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## HISTORICAL REVIEW

Diphtheritic infection of the skin, a rarity in civilian dermatologic practice, has been noted with considerable frequency among the armed forces of various countries during the present war and may be considered a not uncommon military dermatosis in certain geographic areas where diphtheria is more or less endemic and climatic conditions are favorable. These areas include the south of Europe, the Near and Middle East, India and the coasts of Africa. This increase of cutaneous diphtheria in the current conflict parallels in a most interesting fashion a similar outbreak during World War I, when Scott<sup>1</sup> and Manson-Bahr<sup>2</sup> separately noted a sharp rise in the number of cases of so-called veld or desert sore among British troops, resulting in a considerable amount of disability in Egypt, the Near East and at Gallipoli. The latter author pointed out that at least in 1 instance the outbreak of veld sore was incident to a widespread epidemic of faucial diphtheria and in 27 per cent of this group typical diphtheritic paralysis subsequently developed. Later Craig<sup>3</sup> in his classic work on the Sinai peninsula was able to isolate the Klebs-Loeffler bacillus in 67.5 per cent of his series of cases of desert sore, although unfortunately, the virulence of the organism was not determined. In 1917 Fitzgerald and Robertson<sup>4</sup> made a clinical diagnosis of acute cutaneous diphtheria subsequently confirmed by culture in a returned soldier at a Toronto military hospital. They then carried

out a careful bacteriologic study of a series of sixty-seven resistant skin lesions, and were able to demonstrate *Corynebacterium diphtheriae* in 32 cases. Barber and Knott<sup>5</sup> studied an unusual chronic ulceration of the skin involving the left wrist and leg of a soldier, which proved to be caused by infection with an atypical diphtheria organism. In the interim between the two wars Bensted,<sup>6</sup> reporting an epidemic of acute diphtheria among Indian troops, made the extraordinary observation that 69 per cent of his cases were characterized by cutaneous involvement. In 1940 a rather severe outbreak of diphtheria occurred in the British forces in northern Palestine, the identical site of its appearance in epidemic form a quarter of a century earlier among troops of the same nation. This epidemic was described in considerable detail by Cameron and Muir,<sup>7</sup> to whose comprehensive article I have referred in preparing my article. In this instance also an outstanding feature was the large number of cases of a cutaneous variety, comprising more than one third of the total number reported. MacGibbon<sup>8</sup> in a series of 71 cases among allied troops in the Middle East noted 12 of the nonrespiratory variety. He stated that any form of wound, desert sore or cutaneous lesion is liable to become infected with the diphtheria bacillus, and he emphasized the important fact that cutaneous diphtheria, being easily overlooked, is a dangerous focus for the persistence of an epidemic, and suggested that all

1 Cited by Strong R P. *Stutt's Diagnosis, Prevention and Treatment of Tropical Diseases*, Philadelphia: The Blakiston Company, 1942.

2 Manson-Bahr P H. *Manson's Tropical Diseases*, 11th Baltimore: Williams & Wilkins Company, 1941, 680.

3 Craig C M. Veldt Sore Among European Troops. *Lancet* 2:478 (Sept 13) 1919.

4 Fitzgerald I G and Robertson D E. Report on Outbreak of Diphtheritic Wound Infection Among Returned Soldiers. *J A M A* 69:791 (Sept 8) 1917.

5 Barber, H W, and Knott, F A. Chronic Ulceration of the Skin Involving Wrist and Left Leg in a Soldier Due to Infection with an Atypical Diphtheria Bacillus, *Brit J Dermat* 32:71 (March) 1920.

6 Bensted, H J. Limited Outbreak of Diphtheria Exhibiting Both Cutaneous and Faucial Lesions, *J Roy Army M Corps* 67:295 (Nov) 1936.

7 Cameron, J D S, and Muir, E G. Cutaneous Diphtheria in Northern Palestine, *Lancet* 2:720 (Dec 19) 1942.

8 MacGibbon T A. Diphtheria in Middle East: Some Observations on Seventy-One Cases, *Edinburgh M J* 50:617 (Oct.) 1943.



patients with intractable dermal lesions during an epidemic should be treated by large doses of antitoxin or antitoxin plus toxoid. Biggan<sup>9</sup> observed that cutaneous diphtheria in the anal region is more serious than the ordinary variety and may present a definite hazard among mounted troops in the desert, resembling as it does in its initial appearance a thrombosed hemorrhoid. A most impressive recent report on the mounting frequency of cutaneous diphtheria is that of Williams, a British health officer in charge of an isolation hospital for returning soldiers. He discovered virulent bacilli in 12 cases of resistant dermatoses which had previously been diagnosed as impetigo, seborrheic dermatitis, pyoderma and syphilis. In most instances the usual characteristics of these diseases were preserved, and suspicion of their true nature was aroused by persistence of the lesions in spite of vigorous treatment. Williams<sup>9</sup> emphasized strongly the necessity for more frequent bacteriologic investigation in such cases. Response to diphtheria antitoxin was rapid and gratifying. Finally, the importance of the subject was recently emphasized anew by Major J. D. Myers, Medical Corps, United States Army, in an excellent article published in 1944 in a restricted bulletin of the Office of the Surgeon of the European Theater. Outbreaks in Central Europe have also been reported by Weigmann<sup>10</sup> and other German writers.

#### DESCRIPTION OF CUTANEOUS DIPHTHERIA

Diphtheria of the skin exists in two forms: a rare, acute variety almost invariably associated with faucial or nasal diphtheria, consisting of a solitary lesion which may develop on an intact or previously abraded site, and a chronic form, characterized by multiple indolent lesions which occasionally develop from the acute type, but more commonly result from superinfection by *C. diphtheriae* of preexisting dermatoses such as pyodermas, scabies and fungous infections.

The acute or primary variety arises by direct transfer of the organism from an active focus, and the lesions are therefore usually confined to the upper extremities, especially the hands and fore-

arms. The earliest lesion according to Cameron is a small, perifollicular vesiculopustule. This ruptures in a short time, leaving a shallow, superficial ulceration. At this point the base may appear healthy and the edge show no evidence of inflammatory reaction. Later a grayish pellicle forms at the base and the process continues to extend peripherally into normal tissue. The base becomes necrotic and the surrounding tissue undergoes a discoloration ranging from gray to dusky red. Diagnosis is made by demonstration of virulent Klebs-Loeffler bacilli in almost pure culture.

The chronic form is usually found unassociated with active respiratory diphtheria but its incidence mounts rapidly during outbreaks of the



Appearance of lesion in axilla on second day of hospitalization

faucial variety, when contacts with active cases and carriers are frequent. After a few weeks the chronic diphtheritic ulcer presents a punched-out appearance and assumes a circular, oval or more bizarre shape, depending on the nature of the preexisting lesion. The rolled edge is firm, undermined and an unhealthy bluish purple, the base is deep, covered as a rule by a dirty-gray sloughing surface. At times a dark, adherent, leathery membrane forms, beneath which there may be a small quantity of free pus. It is this type of lesion which has given rise to considerable confusion in nomenclature and diagnosis. As Sams<sup>11</sup> emphasizes, the so-called tropical sore may be dermal leishmaniasis, staphylococcal or streptococcal infection, or it may be a dermal diphtheria. He points out that these sores occur most frequently in geographic regions where

<sup>9</sup> Williams, H. C. M. Cutaneous and Conjunctival Diphtheria. Series of Cases, *Brit. M. J.* **2**: 416 (Oct. 2) 1943.

<sup>10</sup> Weigmann, F. Bakteriologische Untersuchungen über Wunddiphtherie, *Bull. Hvg.* **18**: 763 (Sept.) 1943.

<sup>11</sup> Sams, C. F. Medical Problems in the Middle East, *Ann. Int. Med.* **21**: 215 (Aug.) 1944.

there is prolonged exposure to heat with resultant lowering of resistance to all types of infection, where the slightest scratch is prone to develop into a chronic sore. It must be emphasized that a diagnosis of this type of cutaneous diphtheria cannot be made by the appearance of the lesion alone. In a mixed infection the isolation of *C. diphtheriae* is frequently a difficult problem since it may be outgrown by the more luxuriant pyogenic organisms or may be hidden under the adherent base. Cameron and Muir, and Myers stress the necessity for cleansing the suspected lesions with saline compresses before cultures are made. Repeated testing may be necessary to establish a diagnosis. Neglect of these precautions may conceivably account for the discordant findings of one observer<sup>12</sup> who was able to isolate the diphtheria organism in only 2 of 1,000 cases of desert sore.

Although the chronic variety is characterized by a minimum of febrile and other systemic reactions, there have been recorded numerous instances of characteristic late postdiphtheritic complications of a neurologic and myocardial nature. Thus Cameron and Muir observed paralysis of the palate, peripheral nerves and accommodation, and various forms of myocardial degeneration, including heart block. Once these late complications have set in, antitoxin is of doubtful value, and convalescence may be protracted and difficult.

The treatment recommended by all authors, once the diagnosis has been clearly established, is the use of diphtheria antitoxin in fairly large doses. Myers recommended 20,000 to 60,000 units given intramuscularly or intravenously. He states that the local injection of antitoxin in and around the lesion is of dubious value, and this would seem to be the consensus. Local applications, while of secondary importance, help to relieve pain and edema and assist healing. Removal of debris by boric acid or saline compresses may be followed by a sulfonamide ointment. The first reported instance of the local use of penicillin in cutaneous diphtheria is described in this paper.

#### REPORT OF CASE

*History*.—A 31 year old American soldier of Finnish descent was admitted to Gardner General Hospital on August 13, 1944 with the complaint of general malaise and sore throat of seven days duration. He had returned

to the United States from Italy ten days prior to admission, on a routine furlough, following lengthy service in the Mediterranean theater.

The past history was not relevant, the patient denied having had diphtheria or any other communicable disease in childhood. He stated definitely that he had never received immunization against diphtheria. A personal peculiarity of importance in the history was the patient's habit of sleeping with his head on the right shoulder with the arm abducted.

The present illness began three days following his arrival in this country with a mild sore throat. A day or two later he noted an irritation of the skin in the right armpit. These symptoms gradually grew worse as he traveled home, and the family physician after examining the throat made a diagnosis of acute tonsillitis. There was no improvement from medication with sulfonamide compounds, and hospitalization was recommended. On admission the patient did not appear acutely ill, his temperature was 99.4 F and the pulse rate 90. The throat showed enlarged, cryptic tonsils covered by a thick, grayish membrane limited strictly to the tonsillar tissue. The membrane was firm and adherent and removal resulted in bleeding points. Moderate cervical adenopathy was present. Further exposure of the patient revealed an unusual lesion in the right axilla at the edge of the sparse, hairy area at the anterior axillary line. This consisted of an elliptic superficial ulceration about 2 cm × 1.5 cm, the base of which presented a grayish membrane. This membrane likewise could be removed with difficulty, leaving a bleeding surface. Surrounding the lesion for about 1 cm was an areola of grayish discoloration of the skin, and this in turn merged into a zone of dusky erythema. There was moderate swelling of the adjacent tissues, and the axillary glands were slightly enlarged and tender. The patient stated that although this lesion was sensitive, it had not been treated by local application. A tentative clinical diagnosis of acute faucial and cutaneous diphtheria was made, and this was later confirmed by bacteriologic examination.

*Treatment and Course*.—Thirty thousand units of diphtheria antitoxin was given intramuscularly on August 13 and another 28,000 units the following day. In addition, the axillary lesion was treated by local wet applications of 2,500 units of penicillin every three hours. Within twenty-four hours the temperature had fallen to normal, and the throat cleared slowly but completely within seven days. There was a corresponding disappearance of pain and swelling in the axillary region within forty-eight hours but the cutaneous lesion healed slowly. The membrane gradually disappeared after a few days, but the necrotic base persisted and eighteen days were required for complete healing, with the formation of a fine, thin scar. An electrocardiogram taken on August 29 was suggestive of "toxic myocarditis," but two subsequent electrocardiograms were considered within normal limits. Since cultures of the throat were persistently positive, it was treated with penicillin sprays. No further complications developed and on September 19 the patient was discharged as cured.

*Bacteriologic Examination*.—The complete bacteriologic studies of Capt. E. R. Eselius, Sanitary Corps, United States Army, are herewith appended. Smears

<sup>12</sup> Rapport H. M. Desert Sores, Brit. M. J. 2:96 (July 25) 1942.

taken from throat and skin showed gram-positive, straight and slightly curved rods, frequently swollen at both ends, typical of *C diphtheriae*. The organism had the power of fermenting the following substances: dextrose, dextrin, levulose and maltose, galactose and glycerol were not fermented. These findings correspond with the fermenting powers of *C diphtheriae*, Park and Williams, type I—American (no 8). The biochemical reaction was acid in dextrose, dextrin, levulose and maltose, there was no action in galactose, glycerol and saccharose. The organism grew in typical colonies on blood agar, and in three days pure cultures were obtained in Loeffler's blood serum. Two guinea pigs were inoculated subcutaneously with 2 mm of forty-eight hour culture in dextrose veal broth, one culture was taken from the throat lesion and the second from a cutaneous lesion. The animals died within four and three days, respectively. Autopsy revealed hyperemia and congestion of the adrenal glands. The organism was recovered from the site of inoculation and from the blood.

## SUMMARY

1 Diphtheritic infection of the skin is relatively common during wartime. The resistance to treatment of many dermal lesions in subtropical areas may be due to secondary infection with *C diphtheriae*.

2 A definite diagnosis of this entity can be made only by culture and virulence tests, in order to rule out pseudo *C diphtheriae* infection.

3 Although systemic administration of diphtheria antitoxin is the specific therapy in this disease, local applications may be beneficial. Penicillin applied in this manner was judged to be of considerable value in a case of the acute variety herein reported.

# Abstracts from Current Literature

EDITED BY DR HERBERT RATTNER

ORAL MONILIASIS IN NEWBORN INFANTS NINA A ANDERSON, DOROTHY N SAGE and E H SPAULDING, Am J Dis Child 67:450 (June) 1944

The mouths of one hundred and seven newborn infants were examined for Monilia by culturing oral swabs. Fifty-seven mothers were examined for the presence of Monilia by vaginal swabs taken just before or after delivery. Six specimens were taken from each infant at regular intervals from 12 hours of age to the ninth or tenth day of life.

From these studies the authors note that Monilia albicans was isolated, without exception, from each infant who had oral thrush. Oral thrush occurs earlier and appears more frequently in infants whose mothers had vaginal thrush. Finally, for practical purposes, a direct smear containing a yeast from the mouth of a newborn infant which appears clinically to have early thrush may be considered to be positive evidence of oral moniliasis.

NELSON PAUL ANDERSON, Los Angeles

FACTORS INFLUENCING FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS DUE TO SMALLPOX VACCINATION (VACCINIA) GRANT O FAVORITE, Am J M Sc 208 216 (Aug) 1944

Favorite reports on the results of serologic study of 525 recently vaccinated persons. A summary is based on the results of a single test thirty days after vaccination. 22 per cent had weakly positive serologic reactions among 270 persons with immune vaccinia reactions, 73 per cent had positive reactions among 205 persons with accelerated reactions, and 26 per cent had positive reactions among 50 with primary reactions. He concluded that an immune response to smallpox vaccination can be disregarded as a significant cause of a false positive serologic reaction for syphilis. The vast majority of the reactions were doubtful or weakly positive and disappeared within sixty days.

Suggestive observations are presented to show (a) that recently vaccinated persons do not have a reactivation of their positive reactions following typhoid and tetanus immunizations later and (b) that persons with a false positive reaction when revaccinated for smallpox may again present a positive response for syphilis, even though the second reaction is of the immune type. Positive serums stored at 4 C for seven months had a variable decrease of titer, not sufficient to be of differential diagnostic value.

LINCH, St Paul

PREVENTION OF IMPETIGO NEONATORUM. A CLINICAL STUDY OF VARIOUS METHODS INCLUDING THE USE OF A NEW ANTISEPTIC BABY LOTION. CARL C FISCHER Arch Pediat 61 352 (July) 1944

The problem of prevention of epidemics of impetigo neonatorum has been a major one in hospitals for many years. The quest for a satisfactory solution to this problem is still going on.

In reviewing the literature for the past twenty-five years, the author finds that the suggestions to solve this problem fall into two main groups: (1) those which

detail various techniques designed to minimize the possibility of infection of the skin of the newborn infant by causative agent or agents of this disease ("no bath technic" by elimination of trauma of daily cleansings), (2) those which recommend the use of various antiseptics to protect the skin of infants against such infections (external antiseptics, ointments such as ammoniated mercury, sulfanamide compounds and antiseptic oils the antiseptic action of which depends on hydroquinone, hydroxyquinoline or chlorobutanol present in oils).

It is generally agreed on in the prophylaxis of this infection that the best results would follow the use of (1) a technic which would minimize traumatization of the skin of newborn infants as much as possible and (2) an antiseptic agent which has the advantages of (a) easy application, (b) freedom from irritative and sensitivity reaction and (c) ability to inhibit the growth of infecting organisms.

In the author's comparative study of three methods of prophylaxis against this disease over a period of seven years on more than 4,000 infants, including premature infants, he showed that there was a material decrease in the incidence of infection by use of a modification of the "no bath technic" in which no attempt was made to remove the vernix caseosa or otherwise cleanse infants' skins and that an antiseptic lotion (containing cetyl trimethyl ammonium bromide) be applied freely from birth, with special attention to groins, axillas and folds of the neck. The emollient preparation (lotion) can be applied with less trauma. Patch tests and other tests with various dilutions of the active antiseptic ingredient in the lotion showed that it was not irritating and did not produce sensitivity reactions.

GELBER, Los Angeles

CUTANEOUS LEISHMANIASIS DAVID BALL and RAYMOND C RYAN, Bull U S Army M Dept, August 1944, no 79, p 65

This report is based on 499 proved cases of cutaneous leishmaniasis in American forces in the Middle East. Cutaneous leishmaniasis is a granulomatous, ulcerative lesion caused by a protozoan parasite, Leishmania tropica, which is identical morphologically and culturally with Leishmania donovani, the causative agent of kala-azar. The sandfly (Phlebotomus) is the probable vector. The disease is limited to the skin and never causes any constitutional symptoms or general dissemination. The lesions are commonly found on the exposed surfaces, such as the face and arms. The early lesion resembles an indolent insect bite, it is painless, begins as a small red papule and gradually enlarges. Ulceration occurs in the center of the lesion and leads to the formation of a thick crust. The investigators found that a positive diagnosis is best made from smears of scrapings from under the edge of the crust. In untreated patients spontaneous healing begins after three months to one year.

Of the 499 patients admitted for treatment, 102 changed their station, leaving 397 for continued observation and treatment. It was found that the incubation period ranges from ten days to six weeks.

Four methods of treatment were used (1) local treatment consisting of topical application of solid carbon dioxide, (2) local injection of 2 cc of a 1 per cent solution of berberine sulfate into the edges of the sores, (3) intravenous injection of neostam or neostibosan, fifteen doses on alternate days, the first dose 0.2 Gm and subsequent doses of 0.3 Gm, (4) low voltage roentgen therapy. Two hundred and twenty-one patients were treated with neostam intravenously, of which number 207 were cured and 14 remained under treatment at the time the report was made. The minimum time required for cure was two weeks, the maximum, twenty weeks, and there were no failures. When berberine sulfate was used locally 31.8 per cent failed to respond. There were 87.7 per cent failures of response to ethyl chloride spray treatment. The routine roentgen treatment consisted of four treatments of each lesion every four days, the initial dose was 60 r and each succeeding dose was 75 r, a total of 285 r at 90 kilovolts with 1 mm aluminum filter. Of the 28 patients treated with roentgen rays 9 were cured. The results from the local use of neostam were disappointing.

The authors recommended the use of a sandfly net, a headnet and insecticides in known endemic areas as a prophylactic measure.

VACCINIA OCCURRING AT SHORT INTERVALS. CARI A. MINNING, Bull U S Army M Dept, August 1944, no 79, p 82.

Seven hundred and seventeen officers and enlisted men were vaccinated by the multiple pressure method. All men were inoculated with cowpox virus of the same lot number. When the results of these vaccinations were recorded, it was found that vaccinia had been induced in 12 men who had experienced the same condition from ten to fifteen months previously. These men in all probability acquired only transient immunity to smallpox through the first attack of vaccinia. The author therefore concluded that if the spread of smallpox is to be prevented, in addition to periodic vaccinations, there should be routine inoculation with cowpox virus of all persons exposed directly or indirectly, irrespective of the recency or of the results of previous vaccinations.

ASYMPTOMATIC NEUROSYPHILIS. PAUL A. O'LEARY, J. E. MOORE, HARRY C. SOLOMON, JOHN H. STOKES and EVAN THOMAS, Bull U S Army M Dept September 1944, no 80, p 46.

This is the first of a series of three articles on neurosyphilis. The authors discuss the significance of asymptomatic neurosyphilis and stress the importance of an adequate examination of the spinal fluid which should consist of five tests (cell count, complement fixation test, colloidal gold test, estimation of total protein and estimation of globulin).

The significance of the results of the examination of the spinal fluid in prognosis and treatment is then discussed. It is also emphasized that persistently positive serologic reactions of the blood are often due to the presence of asymptomatic neurosyphilis.

FALSE POSITIVE SEROLOGIC REACTIONS FOR SYPHILIS. REPORT OF 100 CASES FOLLOWING ROUTINE IMMUNIZATIONS AND UPPER RESPIRATORY INFECTIONS. A. B. LOVEMAN, Bull U S Army M Dept, September 1944, no 80, p 95.

One hundred cases of false positive serologic reactions for syphilis are reported. A careful study of these cases revealed that the reactions were probably a result of

both Army immunizations and infections of the upper respiratory tract. Loveman, however, felt that the immunizations played a more important role than did the infections. It was found that no one serologic test had an over-all superiority over the other in differentiating true from false positive reactions. The Kahn test, however, proved less dependable than did the Wassermann. In the series reported the Kahn test remained positive for a longer period than did the Wassermann. It was observed that serologic false positive reactions for syphilis may remain positive for six months or longer.

The Kahn quantitative titer was of definite value in differentiating true from false positive types of reactions. Although not universally true, a high titer usually indicated a true syphilitic type of reaction, whereas a low titer was more in favor of a false positive biologic reaction. The gradual diminution of the titer without specific therapy practically always presaged an eventually negative test and thus indicated a false positive reaction.

STRAKOSCH, Denver

INFLUENCE OF HORMONES ON LYMPHOID TISSUE STRUCTURE AND FUNCTION. THE ROLE OF THE PITUITARY ADRENOTROPHIC HORMONE IN THE REGULATION OF THE LYMPHOCYTES AND OTHER CELLULAR ELEMENTS OF THE BLOOD. THOMAS F. DOUGHERTY and ABRAHAM WHITE, Endocrinology 35:1 (July) 1944.

Recent studies suggest one of the mechanisms by which the endocrine organs may influence the bodily reaction to disease. Dougherty and White conclude that the regulation of the numbers of lymphocytes, and probably of red cells in the blood, is under pituitary control and is mediated by way of the adrenal cortex. Their chief evidence is the results of studies in which single injections of pituitary adrenotrophic substance in mice, rats and rabbits produced within a few hours an absolute lymphopenia and an increase in polymorphonuclear leukocytes. Injections of adrenal cortex extract, adrenal cortex steroids in oil and of corticosterone also produced a lymphopenia in intact and in adrenalectomized animals.

LANCH, St Paul

RED BLOOD CELL PASTE IN TREATMENT OF ULCERS AND CHRONICALLY INFECTED WOUNDS. CLIFFORD K. MURRAY and C. M. SHAAR, J A M A 125:779 (July 15) 1944.

The red blood cells which remain after plasma has been aspirated are used for the preparation of a red blood cell paste. The wound is cleansed with isotonic solution of sodium chloride and with dry gauze. The paste is then applied with sterile cotton applicators. Sixty-six patients have been beneficially treated with this paste. Four patients did not respond to treatment. Of 10 varicose ulcers treated by this method only 1 failed to heal. The mode of action of the red blood cell paste is undetermined. The most plausible theory is that proteins or other required nutritional elements are supplied to tissue which, because of inadequate circulation, may be deficient in these substances.

PENICILLIN IN THE PREVENTION AND TREATMENT OF CONGENITAL SYPHILIS. J. W. LENTZ, NORMAN R. INGRAM JR., HERMAN BEERMAN and JOHN H. STOKES, J A M A 126:408 (Oct 14) 1944.

Fourteen pregnant women with early syphilis and 9 infants with congenital syphilis were treated with penicillin. For pregnant women a dose of 2,400,000 Oxford units given intramuscularly round the clock in approxi-

imately eight days is recommended. Therapeutic or placental shock may occur. It may be avoided by considerably reducing the dose for the first thirty-six to forty-eight hours of therapy.

Infants with congenital syphilis responded well to a dosage of approximately 18,000 units per pound (36,000 units per kilogram) of body weight. Grossly infected syphilitic infants, however, may be injured by the injudicious use of penicillin.

EFFECTS OF TETRYL E. W. PROBST, M. H. MUND and L. D. LEWIS, J. A. M. A. 126 424 (Oct 14) 1944

Cutaneous irritation was found to be a common complaint of tetryl workers, an average of 4 per cent having been found to have dermatitis. Four hundred and four cases of tetryl dermatitis were studied. In general, age, sex and color had no influence. It was noticed that most of the reactions occurred in new workers one to two weeks after their introduction to tetryl. In some persons a cutaneous irritation developed in a few moments, while others required several weeks or even months of exposure before a rash appeared.

The face was found to be most frequently affected. The neck was involved in many cases. The extremities were less frequently involved. These cases occurred at points of friction such as the wrists or ankles and extensor surfaces of the forearms. A typical contact dermatitis as a rule progressed to a papulovesicular stage and then became brawny, followed by scaling and some discoloration of the skin. Subjects did not appear to develop any immunity or "hardening" on repeated exposures. By removing all workers from exposure until treatment was completed, all but a small group of allergic persons were ultimately returned to their regular jobs. All patients were treated with boric acid ointment, those with more severe eruptions were treated with 5 per cent sodium bicarbonate wet dressings followed by boric acid ointment.

TREATMENT OF MULTIPLE FURUNCULOSIS WITH PENICILLIN ROSI COLEMAN and WALLACE SAKO, J. A. M. A. 126 427 (Oct 14) 1944

Six cases of multiple furunculosis in young children are reported, with rapid disappearance and cure following treatment with penicillin.

ALLERGY TO PENICILLIN LEO H. CRIFF, J. A. M. A. 126 429 (Oct 14) 1944

A case of allergy to penicillin manifested by generalized severe urticaria is reported. Allergy to penicillin is probably unrelated to sensitivity to penicillin spores. There seemed to be evidence of the presence of some immune substances in the serum of this patient, such as reagins and precipitins, proved by the positive results of a direct cutaneous test by the positive passive transfer and the positive result of a precipitin test.

minimum of 40 mg. Two thirds of the patients were given concomitant weekly injections of a bismuth compound. Four patients died.

Injections of mapharsen alone without bismuth gave poor therapeutic results.

Treatment was given for nine to twelve weeks. Probable "cures" were obtained in 85 to 90 per cent of cases of early syphilis.

INTENSIVE ARSENOTHERAPY A. BENSON CANNON, JEROME K. FISHER, JUAN I. RODRIGUEZ, GUILA F. BEATTIE and EUGENIA MACHLING, J. A. M. A. 126 544 (Oct 28) 1944

Three hundred and thirty-two patients with early syphilis were treated with massive doses of arsphenamine by the syringe method, the period of treatment being five to six days. There was 1 death from toxic hepatitis. Of 178 patients followed for six months to approximately three years, 118 have remained clinically cured.

The authors are of the opinion that this method of treatment is ineffective, dangerous, expensive and altogether impractical. They are convinced that the five or six day intensive treatment plan with arsphenamine must be followed by additional therapy with a heavy metal, fever or both to be successful.

COMBINED TETRYL AND ARSENOTHERAPY IN THE INTENSIVE TREATMENT OF EARLY SYPHILIS EVAN W. THOMAS and GERTRUDE WEXLER, J. A. M. A. 126 550 (Oct 28) 1944

Thomas and Wexler advocate a maximum single dose of mapharsen per day of approximately 1 mg. per kilogram of body weight and a minimum period of treatment of ten days. With this schedule the average patient received ten daily injections of about 60 mg. of mapharsen. To reinforce treatment with this low dosage, four fevers induced by typhoid vaccine were included in the ten days.

There was but 1 fatality in the 1,181 treatment courses given. Four hundred and thirty-five patients were followed six to thirty-eight months. Satisfactory results were obtained in 80.7 per cent.

MASSIVE ARSENOTHERAPY FOR SYPHILIS UNITED STATES PUBLIC HEALTH SERVICE EVALUATION, COOPERATING CLINICS OF NEW YORK AND MIDWESTERN GROUPS J. A. M. A. 126 554 (Oct 28) 1944

Results in a group of 5,351 massive arsenical treatments for syphilis have been studied. The best results followed the use of multiple syringe injection of mapharsen combined with typhoid vaccine. In treatment of primary syphilis the results were 85 to 90 per cent satisfactory, of secondary syphilis, 70 per cent satisfactory. Acute encephalopathy was observed in 0.71 per cent of persons treated, almost half of these (0.32 per cent of the entire group) died.

HENSCHKE, Denver

STUDIES ON LYMPHOGRANULOMA VENEREUM II. THE ASSOCIATION OF SPECIFIC TOXINS WITH AGENTS OF THE LYMPHOGRANULOMA-PSITTACOSIS GROUP GEORGE RAKE and HELEN P. JONES, J. Exper. Med. 79 463 (May) 1944

Rake and Jones suspected that the agent of lymphogranuloma venereum and closely allied agents should be



separated from true viruses and established in a separate group, comparable to the rickettsias, for example. They also suspected that the agent of lymphogranuloma venereum produces a toxin because the clinical symptoms are those of a toxemia. Experimentally, it was possible to demonstrate for three members of the lymphogranuloma-psittacosis group of agents the presence of a factor rapidly fatal to mice. Similar toxins are associated with the agents of meningopneumonitis and mouse pneumonitis. They are labile and are not readily separated from the bodies of the agent. They kill mice rapidly after intravenous injection, and characteristic lesions are found especially in the liver. There was much to relate the toxins to bacterial endotoxins. Antitoxic serums which are effective against a few lethal doses of the toxin were produced in rabbits. The toxins and antitoxins appear to be highly specific, and they may offer a useful tool in distinguishing between different members of this closely interrelated group.

THE EFFECT OF CHEMICAL CARCINOGENS ON VIRUS-INDUCED RABBIT PAPILLOMAS. PEYTON ROUS and WILLIAM F. FRIEDEWALD, *J. Exper. Med.* **79** 511 (May) 1944.

Rous and Friedewald demonstrated that the application of methylcholanthrene and tar to virus-induced papillomas of the domestic rabbit caused them to become carcinomatous with great rapidity and the malignant changes were frequently multiple. The evidence seemed to indicate that the chemical carcinogens acted by way of the virus.

LYNCH, St. Paul

A SPECIFIC CUTANEOUS REACTION IN PERSONS INFECTED WITH THE VIRUS OF HERPES SIMPLEX. F. P. O. NAGLER, *J. Immunol.* **48** 213 (April) 1944.

Recent work on herpes simplex has shown that primary infection with the virus normally takes place in early childhood. The virus then remains latent, presumably in the cells at or near the site of primary infection, i. e., in the buccal mucosa or in the circumoral skin. Under the stimulus of some other infection or even on exposure to excessive light, heat or cold the virus is activated and the familiar vesicular lesions develop. The virus is readily isolated from the vesicular fluid. It is probable that once infection has occurred it persists throughout life. The subject is liable to recurrent attacks of herpes, although the stimulus necessary to provoke an attack varies enormously in different infected persons. All herpetically infected persons, however, show a constant high level of neutralizing antibody in the circulating blood, and the demonstration of this antibody by the chorioallantoic inoculation method is a convenient method of recognizing herpes-infected persons.

Cutaneous tests with influenza virus reagents suggested that the method might also be applicable to herpes simplex. There are many epidemiologic problems in regard to herpes that are still unsolved, and a simple cutaneous test would be particularly valuable if it could provide evidence of past infection in children without the necessity for securing and testing serum. The author found in the course of his experiments that when a heated inactivated preparation of herpes simplex virus is inoculated intracutaneously in herpetic persons a specific erythematous reaction is produced. A positive intracutaneous reaction is regularly correlated with the

presence of circulating antibody against herpes virus. An instance of primary herpetic infection in an adult is reported.

THE ACTION OF PENICILLIN ON THE STAPHYLOCOCCUS IN VITRO. LOWELL A. RANTZ and WILLIAM M. M. KIRBY, *J. Immunol.* **48** 342 (June) 1944.

The authors studied the action of penicillin on staphylococci in vitro by photoelectric turbidimetric methods. They found that penicillin is bactericidal for staphylococci and caused lysis of the organisms and that there is a close correlation between the concentration of penicillin and its activity. The number of organisms in the initial inoculum appears to affect the activity of penicillin, but the constituents of the culture medium do not. They demonstrated more than one hundred fold variations in the sensitivity of strains of staphylococci to penicillin.

THE COMPLEMENT-FIXATION REACTION WITH THE ANTIGEN OF LYMPHOGRANULOMA VENEREUM (LYGRANUM). JOHN E. BLAIR, *J. Immunol.* **49** 63 (July) 1944.

In 1940 McKee, Rake and Shaffer described a complement fixation test using an antigen (lygranum) prepared from cultures of the agent of lymphogranuloma venereum in the yolk sac of the developing chick embryo. Complement fixation tests gave positive reactions with well over 90 per cent of serums from clinical patients with lymphogranuloma venereum. Serums from normal persons gave a correspondingly high proportion of negative results. There was complete agreement between the complement fixation reaction and the Frei reaction in the majority of cases of lymphogranuloma venereum studied. A further significant finding of Rake, Grace and their associates was the fact that positive complement fixation with the antigen of lymphogranuloma venereum was also obtained with a high proportion of serums from persons giving histories of exposure to syphilis and other venereal diseases or of sexual promiscuity.

These observations correlate with the known high incidence of positive Frei reactions among persons of known sexual promiscuity or venereal exposure. They suggest the possibility of the existence of unrecognized or subclinical infections with the agent of lymphogranuloma venereum, which may occur intercurrently with the more commonly recognized venereal diseases. Grace and his associates emphasize the greater delicacy of the complement fixation reaction as a diagnostic test. They suggest that the threshold of the serologic reaction may be lower than that of cutaneous sensitivity, making it possible to detect latent or low grade lymphogranulomatous infection which would not be recognized by the Frei test alone. With this in mind, the author performed a series of complement fixation tests with lygranum, using the serums which were routinely submitted for serologic tests for syphilis. He found that in a series of complement fixation tests with the antigen of lymphogranuloma venereum (lygranum) on 800 serums from 744 patients 4 plus fixation was obtained with 28.5 per cent of serums from persons with known histories of venereal exposure, and with 8.5 per cent of serums from persons who were presumably not exposed. When Frei tests were made on patients whose serums gave complete fixation, about one third elicited positive reactions, at least 6 mm in diameter.

CORNBLEET, Chicago

THE EFFECT OF BILE ACIDS ON THE BILIARY EXCRETION OF NEOARSPHENAMINE AND MAPHARSEN J A ANNGERS, F E SNAPP, A C IVY and A J ATKINSON, *J Lab & Clin Med* **29** 853-862 (Aug) 1944

Because of the extensive use of neoarsphenamine and mapharsen and the occasional occurrence of a clinically evident hepatitis when they are used, the authors considered it worth while to investigate (a) the rationale of the claim that the administration of dehydrocholic acid has a favorable effect in arsenical therapy and (b) the effect of bile acids on the excretion of arsenic. It had been previously reported by other investigators that the administration of sodium dehydrocholate ameliorated the jaundice and anorexia of arsenical hepatitis even when injections of the arsenical were continued and that in rabbits when neoarsphenamine was injected with sodium dehydrocholate less arsenic was recovered from the liver than when the drug was injected alone.

Two types of bile acids were used in the experimentation. One was the conjugated, unoxidized bile acids represented by sodium glycocholate and taurocholate and the other was an unoxidized, conjugated bile acid represented by sodium dehydrocholate. The former preparation is made from cattle bile and causes moderate choleresis but does not increase the hepatic arterial flow, whereas the latter preparation causes a hydrocholeresis and increases the hepatic arterial flow.

The excretion of neoarsphenamine arsenic and mapharsen arsenic in the bile of dogs with permanent bile fistulas was studied under standard conditions with and without the oral administration of sodium glycocholate and taurocholate and sodium dehydrocholate. The dose of neoarsphenamine was 300 mg (60 mg of arsenic), and the dose of mapharsen was 60 mg (17.4 mg of arsenic). The dose of arsenic was given not oftener than once a week. The animals (dogs) weighed from 8 to 12 Kg. The method of Cassil and Wichman was used in the analysis of bile for its arsenic content.

The authors found in the case of neoarsphenamine that an average of 40 per cent of the arsenic administered was recovered in the bile in seventy-two hours. In the case of mapharsen, an average of 40 per cent of the arsenic administered was recovered in forty-eight hours. In both cases most of the arsenic was excreted in the bile during the first twenty-four hour period and only traces were present in the bile after forty-eight to seventy-two hours. Neoarsphenamine arsenic was excreted more slowly by the liver than mapharsen arsenic. Arsenic excreted in the bile was not reabsorbed from the intestine.

It neoarsphenamine arsenic or mapharsen arsenic is excreted by the human liver as by the canine liver, the authors thought it reasonable to assume that an appreciable accumulation of arsenic occurs in the liver, as, for example, when 240 mg of mapharsen is administered daily for five days in massive arsenotherapy. However, in rabbits a sublethal dose may be given weekly without accumulation of arsenic in the liver.

The production of choleresis in dogs does not augment the rate of excretion of neoarsphenamine arsenic or mapharsen arsenic in bile. The administration of sodium dehydrocholate, which causes a brisk choleresis, tends to decrease the elimination of arsenic, and the administration of sodium glycocholate and taurocholate, which cause only a moderate choleresis, tends to increase the elimination of arsenic in the bile.

The simultaneous intravenous administration of sodium dehydrocholate with neoarsphenamine decreases the rate of excretion of arsenic in the bile, though a choleresis occurs, which is probably due to increased passage of the arsenical into the general body tissues secondary to the effect of the bile salts on capillary permeability. If the administration of dehydrocholic acid diminishes the hepatotoxic action of neoarsphenamine and mapharsen it does not do so by increasing their excretion in the bile.

The authors conclude from their investigation that the results do not provide a clear and substantial rationale for the administration of bile acids with arsenicals.

GELBER, Los Angeles

PEMPHIGUS. A FURTHER REPORT ON CHEMICAL STUDIES OF THE BLOOD SERUM AND TREATMENT WITH ADRENOCORTICAL EXTRACT, DIHYDROTACHYSTEROL OR VITAMIN D. W F LEVER and J H TALBOTT, *New England J Med* **231** 44, 1944

No significance can be attached to the reduction in the amount of sodium, chloride, calcium and protein. Thirty-two patients with pemphigus were treated with adrenal cortex extract, dihydrotachysterol or massive doses of vitamin D. The favorable result obtained in some cases of pemphigus vulgaris acutus, pemphigus vegetans and pemphigus vulgaris chronicus are apparently based on the tendency of these drugs to correct the chemical changes. Since the chemical changes are secondary symptoms produced by the disease, the treatment is regarded as merely symptomatic.

RONCHIESE, Providence, R I

## Society Transactions

### CHICAGO DERMATOLOGICAL SOCIETY

LESTER M. WIDDER, M.D., *President*

MARCUS R. CARO, M.D. *Secretary*

Feb 16, 1944

**Neurofibromatosis (von Recklinghausen), Hemangioma of Thigh?** Presented (by invitation) by  
DRS MAURICE OPPENHEIM and DAVID COHEN

Miss I. G., a white woman aged 27, presents numerous red nodules of varying size on the trunk and to a lesser degree on the extremities. They first appeared in 1937. These nodules are not particularly tender. Some are soft and fleshy, others are firm. There are several brown macules on the trunk.

On the right thigh there is an enormous tumor which has been operated on several times, accounting for the large irregular scar.

The Kahn reaction was negative, and the results of urinalysis and a blood count were normal.

#### DISCUSSION

DR OLIVER S. ORMSBY: It is interesting to see a patient with this type of lesion, which is called fibroma pendulum. I have a photograph of a large tumor extending down to the knee. Except for this tumor, the manifestations are those of von Recklinghausen's disease. This added fibroma pendulum makes the case interesting. Nothing can be done therapeutically.

DR MAURICE OPPENHEIM (by invitation): In the dermatologic atlas of Hebra and Kaposi there are pictures of large tumors which hang down from various parts of the body, sometimes over the knees, and are known as fibroma pendulum. This patient was sent to me with a diagnosis of hemangioma cavernosum. I do not believe that this growth is a pure hemangioma cavernosum; I believe that it is a mixed tumor.

### **Papulonecrotic Tuberculid with Latent Syphilis**

Presented by DR EDWARD A. OLIVER and (by invitation) DR SAMUEL M. BLUEFARB

L. P., a white woman aged 37, was first seen on Aug 3, 1943, with lesions on the extensor surfaces of the forearms and legs. The lesions started about five years ago, and since that time she has had several crops of new lesions. The lesions are bilateral and symmetric and start as small papules, they form a crust which soon disappears and leaves a scar. The crop of lesions lasts about six weeks to three months. Tenderness is present at the onset of the new lesions but soon disappears. At present there are no active lesions on the legs.

She has had antisyphilitic therapy for the past four years at the Illinois Social Hygiene Clinic and now at Northwestern University. On Feb 5, 1944 the Wassermann reaction was negative and the Kahn reaction doubtful.

A tuberculin test was made with dilutions of 1:10,000 and 1:100,000. Both elicited strongly positive reactions (4 plus). A roentgenogram of the chest showed normal conditions. There was no clearcut evidence of an old primary tuberculosis in the lungs and no evidence of a

recent or active lesion of any type involving the pleura, pulmonary fields or cardiovascular system. The blood pressure was 100 systolic and 72 diastolic. The urine was normal. The hemogram revealed a hemoglobin content of 13.5 Gm, 3,960,000 erythrocytes and 5,450 leukocytes. The blood sugar level was 88 mg per hundred cubic centimeters, and the blood cholesterol level, 182. Biopsy of one of the lesions near the elbow showed the changes compatible with papulonecrotic tuberculid.

#### DISCUSSION

DR J. H. MITCHELL: The case is interesting to me in view of the stand that Milian took with regard to tuberculosyphilids, namely, that they will respond to treatment.

DR M. H. EBERT: The location and history of the lesions are typical of tuberculid. I think it is impossible to make a diagnosis clinically of the active lesions present today. It is unusual, I believe, to have such a violent reaction to tuberculin. Usually there is a negative anergy with an "id" reaction. In this case it is strongly positive. On looking at the lesion I was reminded of Jadassohn's anetoderma. I could not see enough central necrosis to make a diagnosis of tuberculid. I believe that the section was nonspecific, however, I agree with the diagnosis.

DR S. ROTHMAN (by invitation): I have to disagree with Dr Ebert. In persons with papulonecrotic tuberculid there always is a high degree of sensitivity to tuberculin. There are three forms of cutaneous tuberculosis in which the tuberculin reaction is frequently negative. These forms are Boeck's sarcoid, lupus pernio and tuberculosis miliaris disseminata.

DR FREDERICK R. SCHMIDT: I cannot agree with Dr Rothman. The work of many men cited in the *Arzt-Zieler Handbuch on tuberculosis miliaris disseminata* showed that sensitivity to tuberculin is sometimes present in this disease. Clinically I was not impressed. At the present stage of the disease, it is difficult to say anything further.

DR FRANCIS E. SENFAR: I thought the *Handbuch* included tuberculosis miliaris disseminata among the diseases that do not produce reactions.

DR FREDERICK R. SCHMIDT: I thought that the reaction was positive.

DR S. ROTHMAN (by invitation): Tuberculosis miliaris disseminata is histologically characterized by regular tubercle formation and caseation in the center. Biologically, it is classified as a cutaneous tuberculosis with "positive anergy." The tuberculin reaction is either negative or weakly positive (Jadassohn, W., and Martenstein, H., *Klin Wchnsch* 2:1210-1213, 1923, and Peck, S. M., *Arch f Dermat* 158:545-555, 1929).

DR FREDERICK R. SCHMIDT: I am glad to be corrected.

DR S. ROTHMAN: Clinically this form is relatively benign. There is no peripheral spread, no confluence and no deep destruction. In this respect it is similar to sarcoids.

DR C. W. LAYMON, Minneapolis: In my opinion, the degree of positivity of the tuberculin reaction, even when determined by quantitative intradermal test does

not help a great deal in classifying a particular tuberculid. In my experience practically all patients with papulonecrotic tuberculid have reacted strongly to tuberculin. Also, at the University of Minnesota it has not been found that patients with tuberculosis miliaris disseminata tend toward anergy rather than toward the hyperergic state of patients with the micropapular tuberculid, also called the rosacea-like tuberculid.

DR MALRICE OPPENHEIM (by invitation) In persons with papulonecrotic tuberculid one sees every kind of inflammation and infiltration from pure lymphocytic infiltration to typical tuberculous structures. I think that this depends not only on hypersensitiveness of the skin to tubercle bacilli but on the grade of virulence of the tubercle bacillus. In the various forms of tuberculosis of the skin one also observes the so-called isomorphic reaction. In papulonecrotic tuberculid one often sees a tuberculin reaction with the same clinical and histologic picture, and in syphilis and in other chronic infectious diseases the same phenomenon may be observed. The skin responds to the virus with the same symptoms, whether it comes into the skin by natural ways or artificially, from outside.

#### Diffuse Progressive Scleroderma Following Mastectomy and Extirpation of Axillary Lymph Nodes Presented (by invitation) by DRS STEPHEN ROTHMAN and A. B. HENNINGSEN

R. L., a 41 year old woman had a radical mastectomy with removal of the axillary lymph nodes because of a carcinoma of the left breast in December 1941. A month later her left arm swelled, and the skin of the arm became progressively stiff. For two months this process was confined to the left upper extremity, the lymph drainage of which had been impaired by operation. In March 1942 numbness and paleness of the right hand were noted. Since that time the scleroderma has progressed rapidly, and at the present time her face, neck, chest and abdomen and all her extremities are involved. The progression of the scleroderma has been accompanied with a progressively increasing diffuse hyperpigmentation.

The laboratory examination did not reveal any abnormalities. The serum calcium level was 10.2 mg per hundred cubic centimeters, and calcium balance metabolic studies did not reveal any calcium retention. The hematologic examination showed 9,200 leukocytes, with 65 per cent polymorphonuclears, 30 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils, 12.2 Gm of hemoglobin and 4,710,000 erythrocytes. The basal metabolic rate was -5 per cent. No changes were found in the esophagus by roentgen ray examination and esophagoscopy. Roentgenograms of the bones of the extremities showed no pathologic changes. No disturbances of the function of the endocrine glands were found. The Wassermann and Kahn reactions were negative.

#### DISCUSSION

DR RUBEN NOMLAND, Iowa City. I think that this case brings up the question of the classification of scleroderma and the question of acrosclerosis. In this particular case it seems to me that one would be justified in wondering whether or not one should call the disease acrosclerosis. She gives a poor history, with Raynaud-like symptoms. She has scleroderma on the hands, face and chest. However she does not have the atrophy of the skin that is usually found in acrosclerosis. I think acrosclerosis is a variety of scleroderma in which there are Raynaud-like symptoms and

less involvement of the face. I think that her disease could be classified as diffuse scleroderma with involvement of the hands or a special variety of acrosclerosis.

DR S. ROTHMAN (by invitation) I had the same idea as Dr. Nomland had. I thought that this is what the group at the Mayo Clinic calls true diffuse scleroderma as contrasted with "acrosclerosis" (O'Leary and Waisman, ARCH. DERMAT. & SYPH. 47:382-397 [March] 1943). At the same time this patient's case demonstrates that such a distinction cannot be carried out consistently, because the patient also has Raynaud-like symptoms of the hands and fingers. Still, her disease is different from what has been called "acrosclerosis." It started with a solid edema of the left arm, spreading distally from the axilla, the lymph nodes of which had been removed a few months previously. At first I erroneously diagnosed lymphedema and consecutive fibrosis. Shortly after that, the other arm also became involved. The course of events, i.e. mastectomy with removal of axillary lymph nodes followed by scleroderma on the arm of the side operated on is probably just coincidental, but it is a remarkable coincidence.

#### Hodgkin's Disease of the Skin Presented (by invitation) by DRS S. ROTHMAN and C. L. SPURR

Mrs. C. S., a 68 year old white woman never had had any previous serious illness. One year ago she became ill with influenza followed by a severe productive cough for three months. Progressive loss of weight has followed this illness. After the cough had subsided, the patient began to suffer from itching, first in the cubital fossae but soon over the entire body. The pruritus gradually increased in intensity and could not be alleviated by external applications or by injections. The skin became dark progressively. In the last three months the patient lost 44 pounds (20 Kg.) in weight and became so weak that she could hardly walk.

The skin displays a diffuse brownish gray hyperpigmentation and is moderately thickened, with slight lichenification in some areas. The surface is dry. There is generalized lymphadenopathy, with hard enlarged lymph nodes, particularly pronounced in the axillary and inguinal regions. The liver and spleen are enlarged. Roentgenographic examination of the chest and of the gastrointestinal tract revealed no abnormalities.

The examination of the blood showed 3,200,000 erythrocytes, a hemoglobin content of 7.4 Gm per hundred cubic centimeters (hypochromic anemia) and 13,050 leukocytes, with a differential count of 81 per cent neutrophils, 1 per cent eosinophils, 8 per cent small lymphocytes, 3 per cent medium lymphocytes, 6 per cent monocytes and 1 per cent plasma cells. Wassermann and Kahn reactions of the blood serum were negative.

A sternal puncture showed normal activity of the myeloid and erythroid cells but an increased number of medium-sized lymphocytes, as often found in Hodgkin's disease.

Biopsy of an inguinal lymph node revealed destruction of the normal lymph node architecture by a dense infiltrate of abnormal cells. The infiltrate was polymorphous. Its most conspicuous elements were numerous eosinophilic leukocytes and medium-sized giant cells of the Sternberg-Reed type. The predominant type of cell was the large lymphoid, or reticulum, cell. There was coarse fibrotic tissue and an increase in the amount of fine collagenous fibers within the infiltrate. Mitoses were seen in the reticulum cells.

Biopsy of the skin showed a moderately dense infiltrate in the upper part of the corium, separated by a

band of normal connective tissue from the epidermis. The infiltrate consisted of large lymphocytes and single larger cells with subdivision of the nuclei.

#### DISCUSSION

DR L. H. WINER, Minneapolis: I was interested in this case because of the microscopic section of the skin. There are specific and nonspecific lesions in the skin in Hodgkin's disease. Clinically I should have classified this in the category of nonspecific lesions of Hodgkin's disease, but microscopically I was surprised to see lesions resembling Hodgkin's disease. I saw that the infiltrate consisted of cells containing large nuclei and clear cytoplasm, which one can call proliferating reticulum cells. This means a good deal to me in the diagnosis of Hodgkin's disease. I think that this case would fit into the cases of the specific form of Hodgkin's disease of the skin.

DR C. L. SPURR (by invitation): This case was of interest to me because we found an unusual number of lymphocytes in the aspirated sternal marrow. Steiner has recently published his study on the incidence of Hodgkin's disease in the bone marrow. He found that 79 per cent of his cases coming to autopsy showed lymphogranulomatous foci in the marrow. These lesions showed considerable reticular cell hyperplasia, with fibrosis and infiltration with lymphocytes, but no follicles. In view of the nature of the lesion it is unlikely that a diagnostic portion of specific tissue may be aspirated.

#### Granuloma Annulare Presented by DR DAVID V OMENS and (by invitation) DR HAROLD D OMENS

G. K., an American boy aged 7, presents an eruption which has been present for about six months. On both hands and the dorsal surfaces of the arms and legs are several coin-sized patches which are elevated and composed of grouped nodules, the centers of which are depressed, with raised and rolled peripheral edges. These lesions are devoid of any subjective sensation and they seem to progress rapidly.

Histologic examination revealed hyperkeratosis with acanthosis and intracellular edema of the prickle cells, the papillae of the corium were shortened, with dilatation of the capillaries, and in the subpapillary layer of the corium there was a focus of connective tissue necrosis in the center of which were some epithelioid cells surrounded by small lymphocytes and a giant cell in the periphery of this focus. The subpapillary portion of the corium presented dilatation of the blood vessels, which were surrounded by an infiltrate composed of small round cells and numerous plasma cells.

#### A Case for Diagnosis (Granuloma Annulare?)

Presented by DR DAVID V OMENS and (by invitation) DRS HAROLD D OMENS and M. OTSUKA

C. B., a Negro boy aged 3, presents an eruption of various-sized nodules on the lower extremities which started four months ago as a single lesion, with new lesions gradually appearing while the older lesions enlarged in diameter. None of the lesions have disappeared, and the condition is devoid of subjective sensation.

The Kahn reaction and the result of a Mantoux test were negative. Roentgenograms of the long bones and chest showed no evidence of tuberculosis. Examination of the blood showed 96 per cent hemoglobin, 5,096,000 erythrocytes and 9,000 leukocytes.

Histologic examination revealed hyperkeratosis with acanthosis and intracellular edema of the prickle cells of the malpighian layer. The papillae were shortened and broad in some areas and in some areas were completely effaced. In the papillae and the subpapillary layer of the corium the blood vessels were dilated with only a mild perivascular infiltration composed of small round cells.

The condition today shows 50 per cent improvement with tonic therapy.

#### DISCUSSION OF THE PRECEDING TWO CASES

DR M. J. REUTER, Milwaukee: I agree with the diagnosis. It is my impression that the disease occurs primarily in children and that in the course of months or years the lesions disappear. I wonder whether any one else can corroborate this.

DR HARRY R. FOERSTER, Milwaukee: I believe that both cases are examples of granuloma annulare. In some cases this disease in children persists for many years without being influenced by varied therapeutic procedures. In other cases the lesions may disappear spontaneously or after a minimum of treatment. This behavior suggests a low grade nonspecific infection or a moderate toxemia as the etiologic factor.

DR MAURICE OPPENHEIM (by invitation): The case of the 7 year old boy is interesting because it is rare to see so highly developed and livid areas with such a bluish violet color and central depression. Granuloma annulare in children usually has the color of the surrounding skin. What Dr Foerster says is true, that the lesions disappear spontaneously or after superficial treatment. I treat my patients with Grenz rays.

The diagnosis in the case of the younger boy is not so certain, the eruption is much too superficial.

I should like to mention on this occasion that there is no resemblance clinically and histologically between dermatitis atrophicans lipoidica diabeticorum and granuloma annulare. This cannot be pointed out too often. Ellis was the first who believed that these two diseases are identical. I was the first who described dermatitis diabetica, also called necrobiosis lipoidica, but the two diseases can be distinguished very early.

DR FRANCIS E. SENEAR: In the case of the older boy I do not think that there would be any difficulty in diagnosis with the lesions that are present on the upper extremity and particularly the one on the wrist. If one had seen only the lesions on the wrist, much more nodular than usual, I think it would be difficult to make a diagnosis clinically.

Personally, I have not been able to make a distinction between granuloma annulare and necrobiosis lipoidica diabeticorum. I should like to ask whether any one who has had experience with the latter disease would have felt that it might be a tenable diagnosis as an explanation for the occurrence of the inflammatory reaction.

DR FREDERICK R. SCHMIDT: My recollection is that many histologists, among them Jadassohn and Matras, have told me that they consider granuloma annulare and erythema elevatum diutinum one and the same disease.

DR MARCUS R. CARO: In answer to Dr Reuter's remarks, nine years ago I presented to this society a patient with granuloma annulare on the back of the right hand (ARCH. DERMAT. & SYPH., 32:686, 1935). When I saw this patient several months ago she still had the lesion at the same site in spite of repeated treatments with solid carbon dioxide, radium and peel-



ing ointments. There has been involution in the center of the patch, but there has also been a gradual advance of the border. It has not been my experience that in all cases the lesions clear up readily with treatment.

DR JAMES H. MITCHELL: I should like to corroborate what Dr Caro said. The lesions heal when treated with solid carbon dioxide and new ones form. They do not undergo this pleasing result that has been mentioned.

DR D. V. OMINS: I saw the 7 year old boy about two weeks ago and the lesions then were much more elevated than they are today. After biopsy the lesions in that location seemed to recede uniformly. The little Negro child had lesions that were elevated and pronounced. We performed a biopsy and as a placebo gave cod liver oil and since then the lesions have almost disappeared.

#### Sickleemia with Ulcers of the Leg Presented by DR M. H. EMERT and (by invitation) DR M. OSHUKA

G. H., a Negro aged 20, came to the outpatient clinic with a chronic ulcer of the ankle. About one and one-half years ago a dime-sized superficial ulcer developed below the left external malleolus; it healed in three months. Two months later a similar ulcer developed on the medial aspect of the left leg which healed in six months. While this ulcer was active another developed on the right leg. The ulcers heal in about six months but reappear in the same site two or three months later.

The patient has never been seriously ill and has never been hospitalized previously. His father and mother died of unknown causes, when he was 2 years old. He has had no brothers or sisters.

On the inner aspect of the left leg there are two ulcers. The posterior one is 2 by 3 cm., and the upper half is 4 or 5 mm. deep. The floor is necrotic and covered with a yellow membrane. The rest of the ulcer is shallow and granulating. The border is irregular in outline and slightly raised. The other ulcer is shallow, irregular in outline, with a granulomatous floor. It is partially surrounded by the scar of a former ulcer. There is a similar silver quarter-sized ulcer above the right internal malleolus.

Aside from a blood pressure of 152 systolic and 80 diastolic the physical examination revealed nothing significant. The Kahn and Wassermann reactions of the blood serum were negative. There was no evidence of jaundice. The hemoglobin content was 96 per cent, there were 5,000,000 erythrocytes and 8,850 leukocytes. The erythrocytes showed sickling on standing. The blood chemistry and the results of urinalysis were normal. Roentgenograms of the skull, chest and long bones showed no pathologic changes.

A specimen was removed for biopsy from the wall of the deep ulcer, and the sections showed thrombosis of some of the large arteries and pseudocarcinomatous changes in the epidermal tissue.

#### DISCUSSION

DR THEODORE CORNBETT: There was a peculiar brilliant yellowish red color present in these lesions that I have not hitherto seen in this kind of ulcer. Could this tint be imparted by the blood, which has a hemoglobin content of 96 per cent and a red cell count of over 5,000,000?

DR FRANCIS W. LYNCH, St. Paul: Has a satisfactory explanation been offered for the mechanism of develop-

ment of such ulcers as are observed in patients with sickleemia? How may one account for healing, scar formation and subsequent recurrence of ulceration? Vascular changes are evident in the sections presented by Drs. Ebert and Otsuka, but what led to their development?

DR M. H. EMERT: I must say that I am indebted to Dr. Otsuka for his interest in this type of lesion. He has been visiting the wards of the Cook County Hospital in the last two or three weeks and has found 4 cases of ulcer of the leg in Negro patients, 3 with sickleemia and the fourth with hemolytic anemia, all of the same family name. There is supposed to be a familial tendency to this disease, but we were unable to find whether these persons were related or whether the similarity of names was merely coincidence. Please note that I presented the case as sickleemia. I think that this is a better term than sickle cell anemia. This man has no anemia, but the sickling is always present. Dr. Schwartz of the department of hematology at the Cook County Hospital has shown Dr. Otsuka that it is necessary to keep the specimen moist and this is done by a wet pad. The red cells will sickle then when they will not sickle in dry air.

Dr. Schwartz is also interested in the physical makeup of these persons. He points out that in most cases they have peculiar long slender fingers. That is true of the 3 cases that I just spoke of. Whether it is uniformly associated with sickleemia or not I am sure I cannot say.

It is also interesting that this disease was originally described in Chicago. Dr. James P. Herrick described the first case and we are particularly interested, especially in view of the large Negro population. I am sure that I missed many cases of its occurrence in the clinics of the Cook County Hospital in patients with ulcers of the leg. I did not think of sickleemia in regard to the pathogenesis of ulcer. I think that Dr. Lynch made a good point that it is not a question of anemia and that there must be another mechanism. One explanation is that these sickle cells become thrombosed easier in the peripheral vessels. I do not consider that to be the whole explanation because there is too much infiltration in the wall of the vessels.

The other point is that unlike most persons with sickleemia this patient had remarkably good health, and he had no complaints prior to the appearance of the ulcers. He has never had arthritis. Most persons with the disease have episodes during which they have articular and abdominal pains and an absolute anemia develops. We encountered this patient in the outpatient clinic.

#### Glomus Tumor (Tumor Removed Recently) Presented by Drs. D. V. OMINS and M. H. EMERT

This 74 year old white man, A. P., presented a 3 by 3 by 2 mm. sized, reddish blue tumor, extremely tender to the touch, and of eight years' duration, on the inner anterior aspect of the right knee. It was recently removed surgically. It had become annoying and uncomfortable in the past three years. Trigger-like paroxysmal pain was experienced even on walking. There is no history of previous injury to the site of the tumor.

Physically, the patient is essentially normal except for a localized opacity in the right cornea.

Examination of the blood showed 80 per cent hemoglobin, 4,200,000 red cells and 8,650 leukocytes with a



normal differential count The Kahn reaction was negative and blood chemistry was normal The urinalysis was essentially normal

## DISCUSSION

DR MARCUS R CARO I agree with the histologic diagnosis of glomus tumor and I congratulate Dr Omens and Dr Ebert on the excellent result

DR M H EBERT The slides showed nerve fibers in the tumor

### Familial or Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Syndrome) Presented by DR M H EBERT

S A, a white man aged 65, was admitted to the Cook County Hospital because of gradually oncoming weakness and associated secondary anemia Since he has been in the hospital, he has had repeated attacks of epistaxis nearly every day When questioned his relatives stated that he has had these attacks of epistaxis as far back as he can remember and that his mother died from this same condition His two sisters and his daughter have attacks of epistaxis He has received all types of local and internal therapy for these episodes of bleeding

The patient presents multiple pinhead-sized hemangiomas on the upper and lower lips, tongue, hard palate, face and left ear lobe A defect is present on the right anterior side of the tongue from a previous surgical procedure

The examination of the blood revealed 18 per cent hemoglobin, 2,270,000 erythrocytes and 6,750 leukocytes, with a normal differential distribution Microcytosis and poikilocytosis were noted The Kahn reaction was negative and the icteric index was normal, as was the vitamin C level The blood chemistry was essentially normal Roentgenographic studies of the gastrointestinal tract showed essentially normal conditions

## DISCUSSION

DR THEODORE CORNBLEET I should like to ask whether 18 per cent hemoglobin is correct

DR M H EBERT This man is a patient in the medical service, and that was the percentage of hemoglobin when he was first admitted

DR S ROTHMAN (by invitation) There is a relatively slight involvement of the skin and mucous membrane of the mouth It would be interesting to know about the familial involvement Osler's disease is inherited as a dominant, and this patient probably has close relatives who are suffering from the same disease

DR EARLE PACE It was mentioned that everything had been tried from a therapeutic standpoint I wonder if moccasin venom has been used I have under treatment a woman about 30 years old who had two or three severe hemorrhages daily from the nose, tongue and lips With weekly injections of moccasin venom at first and now an injection every two weeks, she is having only occasional hemorrhages and mostly at the menstrual period I am using smaller doses than Peck recommended The nurses who are observing the case insist that the lesions on the face and tongue are shrinking and becoming less conspicuous

DR M H EBERT We have no authority to make changes in the therapy because this man is a patient in the medical ward and is presented through the courtesy of the medical department I think that the suggestions made by Dr Pace are good ones, and I will pass them on to the men in charge

### A Case for Diagnosis (Spiegler-Fendt Sarcoid, Pseudoleukemia Cutis?) Presented by DR S W BECKER and (by invitation) DR N C BARWASSER

J H, a railroad fireman aged 50, noticed the development of hard nodules on the frontal region of the scalp four years ago They resembled the present lesions and cleared with arsenical therapy in three months, slight discoloration was left

Nine months ago lesions appeared in the right parietal region and later in the frontal region and over the entire right side of the scalp They vary from 3 to 6 cm in diameter, are discrete and confluent, are bluish red with telangiectasis on the surface in some areas and have sloping borders and elevated centers up to 0.75 cm The center of a large lesion on the right temple has ulcerated, as has a neighboring lesion About twelve lesions are present Lymphadenopathy was not noted

The patient's general physical condition is good Examination of the blood on February 14 showed 91 per cent hemoglobin, 4,980,000 erythrocytes and 9,950 leukocytes A Schilling differential count showed lymphocytes, 38 per cent, segmented forms, 46 per cent, staff cells, 7 per cent, juvenile cells, 4 per cent, eosinophils, 2 per cent, and degenerated forms, 3 per cent A tuberculin test (0.005 mg tuberculin intracutaneously) elicited a positive reaction

Histologic examination of a specimen removed from a lesion in the right parietal region showed the epidermis to be normal Beneath the epidermis was a narrow band of normal collagen Beneath this band the entire section was infiltrated with lymphocytes, larger mononuclear cells and some cells of the reticulo-cyte variety There were small areas of necrosis

Treatment by means of roentgen rays and sodium cacodylate for one month has been followed by improvement

## DISCUSSION

DR LOUIE H WINER, Minneapolis On examining the histologic section, I was led to believe that this might be primary Hodgkin's disease of the skin, because the section shows areas of fibrosis, eosinophils and multi-form cellular infiltrate

DR MARCUS R CARO I could not make a histologic diagnosis from the section shown The narrow band of corium lying between the epidermis and the infiltrate and the dense cellular infiltrate suggested some type of leukemia I should like to see a section prepared with the Giemsa stain before making a definite diagnosis

DR RUBEN NOMLAND, Iowa City I think that this is leukemia cutis, and I think that the biopsy specimen was not taken deep enough to give the true picture of what is going on I believe that it is probably an aleukemic lymphatic leukemia Since the patient was dressed, we had little opportunity to examine the lymph nodes, but we saw one walnut-sized lymph node in the left anilla This node and the lesions in the scalp cause this patient's involvement to resemble that of 3 patients I have seen with leukemic infiltrations of this kind in the scalp and enlargement of one or several groups of lymph nodes but no leukemic blood picture However, pending a better biopsy I should make a diagnosis of leukemic infiltration in the scalp in a person with aleukemic lymphatic leukemia

DR FRANCIS W LYNCH, St Paul In the light of modern hematologic and histopathologic knowledge, it is difficult to realize exactly what was previously meant by the term Spiegler-Fendt sarcoid It is probably better to avoid use of that term and of pseudoleukemia and admit that the eruption cannot as yet be accurately

diagnosed. In this case, I believe, the eruption should be regarded as leukemia cutis with the expectation that the type of leukemia will be determined later by observation of the course of the disease and by further study of the blood.

DR S W BECKER I saw the slides before I saw the patient. The slides were sent in with a suggested diagnosis of sarcoid. I said that the only type of sarcoid which it could be was the Spiegler-Fendt type, with which I am not very familiar. However, clinically I thought the disease belonged to the leukemic group. I used the term pseudoleukemia simply because Dr Wells used it to signify that the patient has no blood picture of leukemia as yet. The fact that the initial lesion disappeared after treatment with potassium arsenite and that the patient had no further trouble for three or four years I thought was unusual.

DR L F WEBER It is just an unusual syphiloderm to me.

DR E M SMITH JR I should like to ask why there was so much pigmentation around the hair.

**Mycosis Fungoides** Presented by DRS F E SENEAR and M R CARO and (by invitation) DR C H STUBENRAUCH

M W, a white woman aged 28, first consulted a physician in March 1938, because she was pale and felt tired most of the time. One month later a generalized cutaneous eruption appeared. She was seen by a dermatologist in October 1938 and told that her eruption was eczema. A thorough check-up revealed no organic lesions. She was treated with various ointments and with roentgen rays, but by August 1939 her cutaneous picture had not changed. During the next year the patient treated herself with various proprietary ointments, with slight temporary improvement.

In September 1940 she consulted another dermatologist, who made a diagnosis of neurodermatitis and treated her with vitamin B and calcium by injection. Her condition became steadily worse, her legs began to swell, and her hair fell out. During this period she received six or seven treatments with roentgen rays to the face.

In the spring of 1942 the patient was hospitalized at the University of Illinois. At that time she had an extremely severe generalized eczematous eruption presenting almost the picture of an exfoliative dermatitis. There were large platelike scales in some places, while other regions were moist, suggesting a streptococcic dermatitis. By July 1942 nodular lesions began to appear in both involved and uninvolved areas. These lesions were firm, red and discrete. They varied in size from that of a split pea to that of a walnut. From time to time larger, ulcerated, tumor-like lesions appeared. The patient was treated with low voltage roentgen rays and sulfathiazole ointment. There has been a gradual change in the cutaneous eruption from the picture of a generalized eczema to the picture present today.

At the present time there is a generalized eruption consisting of red, slightly elevated plaques and nodules. The lesions are round, oval and serpiginous, soft to moderately firm, discrete and covered with scales.

The Wassermann and Kahn reactions were negative. The basal metabolic rate was  $+35$  per cent. The urine was normal. The hematologic examination showed hemoglobin, 13 Gm, erythrocytes, 4,220,000, and leukocytes, 16,200, with a differential count of 58 per cent neutrophils, 40 per cent lymphocytes and 2 per cent monocytes. A sternal puncture revealed a bone marrow

not diagnostic of any blood dyscrasia. The corrected sedimentation rate was 26 mm per hour.

Biopsies were performed in September 1942, in July 1943, and in February 1944. A biopsy specimen taken from the left shoulder on Sept 1, 1942 showed changes indicative of leukemia. Biopsy of a nodule on the right shoulder on July 27, 1943 showed the histologic changes of mycosis fungoides. A specimen was removed last week from one of the infiltrated patches on the back. There was a moderate degree of acanthosis and slight edema of the epidermis, but the basal layer was intact. In the widened papillae and about the superficial blood vessels there were loose edematous mantles of cells composed largely of lymphocytes, histiocytes and connective tissue cells.

#### DISCUSSION

DR FRANCIS W LANCH I should like to call attention to the elevated basal metabolic rate ( $+35$  per cent), a phenomenon frequently observed in leukemia, sometimes as early evidence of the disease. It might be of interest to determine the rates of patients having mycosis fungoides in an early stage, so that the extent of the cutaneous involvement would not be an important factor.

DR MAURICE OPPENHEIM (by invitation) The clinical aspect of this case is striking. For me the diagnosis of mycosis fungoides is doubtful. The dissemination of the nodules and papules is too regular, their size is too uniform. In mycosis fungoides the dissemination and size of the lesions are much more irregular. I talked with Dr Senear, and he agreed with me that the clinical picture is different from the ordinary clinical aspect of mycosis fungoides. My first diagnosis was leukemia cutis, but the blood count did not suggest leukemia. The absence of eosinophils in the blood count spoke against diagnosis mycosis fungoides. On the other hand, the history of neurodermatitis-like rashes and loss of hair speak more for mycosis fungoides.

DR S ROTHMAN (by invitation) I have to disagree with Dr Oppenheim. I think that clinically this case represents typical mycosis fungoides in the tumor stage, possibly mycosis fungoides d'emblee. An almost identical picture of mycosis fungoides has been published in the atlas of Nekam (Nekam, L. *Corpus iconum morborum Cutaneorum*, Leipzig, Johann Ambrosius Barth, 1938, vol 3, p 651, fig 3347). That the tumors did not develop to "rotten-tomato-like" lesions is obviously due to the roentgen ray therapy.

DR MARCUS R CARO When the patient was first seen in July 1942, a biopsy specimen taken from a lesion on the back showed the histologic picture of leukemia, which was surprising because it did not seem to fit in with the clinical picture. In July 1943 biopsy of a specimen from the shoulder showed the characteristic picture of mycosis fungoides. The specimen taken last week from a lesion on the back again showed the histologic features of mycosis fungoides, but it was not as characteristic as was the specimen of last year.

**Unusual Syphiloderm** Presented by DR M H EBERT and (by invitation) DR M OTSUKA

R B, a white man aged 34, noted the development ten weeks ago of a wide, red, raised, edematous welt extending from the right pubic region to the right trochanter which was tender on pressure. On this area there appeared three large, raised, flat nodules with central crusting. In a few days similar nodules appeared on each side of the pubis. One week later there developed what appeared to be a severe cellulitis of the

right buttock. He was admitted to the surgical service of Cook County Hospital. He had a temperature of 100 F on admission, but it became normal the next day. Dry heat was used. No sulfonamide compounds were given. A week later his penis and scrotum became dull red, intensely swollen and tender. A few days later a group of nodules appeared in the right genitofemoral fold, and later discrete nodules appeared on the face and shoulders. Aside from local discomfort the patient has not felt ill. In September 1943 he had a gonorrheal urethritis which was cleared with 15 Gm of sulfathiazole.

At present the right buttock is purplish red and slightly infiltrated. On the opposing surfaces of the nates extending around the anus there is a large eroded dull red granulomatous plaque with a raised firm border. On the inner surface of the right thigh about 2 inches (5 cm) from the genitofemoral fold there are a number of flat-topped bluish red raised nodules about 1 cm in diameter. Many of these have coalesced, and some are eroded on the surface. The penis and scrotum are bluish red and edematous. In the fold at the base of the penis there is a raw granulomatous surface. On the sides of the scrotum there are several nodules similar to those on the thighs. On the right side of the abdomen there are three dime-sized copper-colored slightly raised nodules. A few raised flat nodules about 6 to 8 inches (15 to 20 cm) in diameter are scattered on the face and shoulders. There is no significant adenopathy. He has had no lesions in the mouth except under an ill-fitting upper denture. Results of Kahn, Hinton and Kahn verification tests were positive. The smears from several lesions stained with the Fontana method showed numerous spirochetes. Cultures made on Saboraud's medium were negative. Potassium hydroxide preparations demonstrated no mycotic infection. Ziehl-Neelsen stains were all negative. Several specimens for biopsy were taken, and the sections showed a plasmonia.

#### DISCUSSION

DR M H EBERT. I had hoped that some one would have some other suggestion. I had some temerity in presenting this case as an instance of syphiloderm. It is true that a dark field examination was not made. We had no facilities for making it. Smears from every type of lesion stained by the Fontana silver method were all positive for syphilis. When I first saw this man in the outpatient clinic he looked altogether different than he does today. The lesions gave the impression of being pustular, but they were not. The centers were eroded and crusted. This extraordinary history of cellulitis extending from the pubes around to the trochanter on the right side and then subsiding, with subsequent development of an intense cellulitis in the buttock and the presence of cellulitis in the genital region are outside my experience in syphilis. However, spirochetes were present, but whether *Treponema pallidum* I cannot say. I expected in some of these lesions we would have some unusual histologic pictures and would be able to demonstrate secondary organisms but that was not possible. The ones I have studied were all plasma cells with no change in the blood vessel wall. I presume this is an unusual syphiloderm. I also expect that a few injections of arsphenamine will clear it up.

NOTE—The patient was at the Chicago Intensive Treatment Center when *Treponema pallidum* was demonstrated. The disease cleared rapidly with intensive therapy.

#### Hyperpigmentation from Prolonged Use of a Mercurial Application. Presented by DR THEODORE CORNBLEET and (by invitation) DR H C SCHIÖRR

R C, a Negro woman aged 30, presents poorly outlined hyperpigmented areas on the forehead, nose, chin and cheeks. The lesions appeared in 1938 and became darker progressively. She had been using a "skin whitener" for ten years prior to the appearance of the skin changes. This application contains 15 per cent ammoniated mercury. Apparently it is used extensively by Negroes as a bleaching agent.

Dark field examination of sections of tissue showed tremendous numbers of brilliant particles. The latter were larger than melanin granules and were entirely different in appearance.

#### DISCUSSION

DR S ROTHMAN (by invitation). I should like to ask whether there is a history of inflammation preceding the hyperpigmentation and whether the lesion could be interpreted as a postinflammatory pigmentation. Whereas mercurial deposits are common following the use of other mercury salts, such deposits seem to be an unusual sequela to the application of ammoniated mercury. From this compound metallic mercury is either not split off at all in the skin or the decomposition of the compound is extremely slow and negligible for all practical purposes.

DR J H MITCHELL. Dr Nomland and I had a patient in the dispensary who had a similar pigmentation due to Novena cream. Biopsy was performed, and I made some dark field pictures which were shown at the meeting of the American Academy of Dermatology and Syphilology and which showed characteristic deposition of mercury around the glands.

DR M H EBERT. I wonder whether it was ammoniated mercury or metallic mercury that was used.

DR EDWARD A OLIVER. Several years ago I saw a woman with irregularly shaped, gray-black pigmented areas about the chin and neck. She consulted me that day about an epithelioma on her face, and when I remarked about the grayish-black areas she stated that they were "liver spots" and that she was taking medical treatment for gallbladder disease. My interest was aroused and I questioned her at length and found that she was using a freckle cream which contained ammoniated mercury. When she discontinued use of the freckle cream, her "liver spots" quickly disappeared.

DR MAURICE OPPENHEIM (by invitation). I agree with Dr Rothman in this case. Negroes use ointments several times a day to grease their skin, and in consequence hyperpigmentation occurs. It is known that long contact with tars and their products causes hyperpigmentation and hyperkeratosis ("tar skin"). The same is true for ointments and lubricants containing derivatives from pteridine and tar. I have never seen hyperpigmentation following the use of a pure mercurial ointment. When I was an assistant in Neumann and Finger's clinic in Vienna and also later, syphilis was treated with mercurial inunctions. I have never seen a pigmentation of the skin caused by the blue 33 per cent mercury-containing ointment. I believe the pigmentation in this case is caused by the ointment base. The cheeks of this woman showed changes like atrophoderma vermiculata, which picture we find often in Negroes and which I consider also as a consequence of the use of petrolatum ointments.

DR D V OMENS. I saw this patient a number of years ago. She has never presented any inflammatory

process on the face except the pigmentation. The body is somewhat lighter than the face.

DR S W BECKER This woman has had some hyperpigmentation in the folds about the nose like that described by Goeckerman years ago following the use of Oriental face cream, which contained mercury. He studied the involved areas histochemically and thought that the skin contained the mercury. That condition would not account for the hyperpigmentation on the forehead, which is melanotic. I believe that she has hydrargyria, which is the condition described by Goeckerman.

DR NORMAN TOBIAS, St Louis (by invitation) I should like to suggest that this patient be examined under the Wood light, which might show the hyperpigmentation to be more extensive than that appearing to the naked eye.

DR THEODORE CORNBLEET In the American dermatologic literature Goeckerman was the first to call attention to this phenomenon. His description was complete and can be called an American classic. Evidently his work has not been appreciated by Continental dermatologists. The individual type of heavy metal deposit is said to give its own distinctive picture by dark field illumination. Tissue sections from a biopsy specimen of this patient's cheek display brilliant granules by this means. Melanin granules cannot be exhibited in this manner, they have poor reflecting surfaces. Because of this, the only difference of opinion possible here is as to which metal is forming the deposit. I do not have enough experience to know the dark field appearance. The patient has been using the same preparation on her cheeks for many years. The label on the jar states it contains a mercurial compound, so the inference is justifiable that the granules in the deposit contain this metal. Undoubtedly there is, in addition, a slight excess of melanin not shown histologically, but that is beside the point. It seems obvious that the clinical discoloration is not due to melanin as such but is a metallic pigmentation of the variety due to absorption and deposition of material from applications.

**Lichen Planus in Husband and Wife** Presented by DR F E SENEAR and DR M R CARO and (by invitation) by DR C H STUBENRAUCH

L Z, a white woman aged 59, was first seen at the University of Illinois Research Hospital two weeks ago. She stated that she had had malaria twelve years ago, and had taken 30 grains (2 Gm) of quinine a day almost continuously since then. She believes that whenever quinine therapy is stopped she becomes ill. Two months ago the patient discontinued quinine therapy and has taken none since. She states that her skin became yellow soon after she took the last dose of the drug. All of the present cutaneous lesions have appeared during the past two months.

On the dorsa of the hands and on the forearms, arms, legs, thighs, hips and buttocks is an eruption consisting of violaceous papules and nodules, many of which are covered with a thick scale. The primary lesions are flat topped and angular. Some of the lesions on the legs are excoriated and crusted. Physical examination otherwise reveals essentially normal conditions except for yellowish brown discoloration of the skin and hypertension. The liver and spleen are not palpable. The results of tests of hepatic function were normal, and the icterus index was within normal limits.

The Wassermann and Kahn reactions were normal, the blood count was essentially normal and the basal metabolic rate was  $+7$  per cent.

The patient's husband, P Z, aged 63, has taken quinine almost daily for one and a half years. He also discontinued its use two months ago. Since that time he has had lesions similar to those of his wife but not so extensive.

Biopsy specimens from both patients showed a histologic picture of lichen planus, that of the wife being of the hypertrophic type.

#### DISCUSSION

DR FREDERICK R SCHMIDT On questioning the woman stated that she has been taking quinacrine hydrochloride. She started taking it before the lesions appeared. Both she and her husband were taking it, though they have stopped it for the past two weeks.

DR F E SENEAR This patient is in the medical service, and I do not know much about the case. When I first saw her, she said that if she could have some quinine she would be able to clear the eruption in two weeks.

DR C W LAYMON, Minneapolis In the case of the woman two possibilities come to mind, lichen planus and prurigo nodularis. I favor the former. The husband's eruption was difficult to diagnose clinically, although lichen planus and lupus erythematosus seemed to be the most likely considerations. In this case the histopathologic conditions were consistent with the former diagnosis.

DR JAMES H MITCHELL Dr Schmidt and I talked to this woman about quinine, and then she admitted that she had been taking quinacrine hydrochloride. We have all seen lichen planus develop during arsenical therapy. It is of great interest to me whether the quinacrine has anything to do with the two cases. I think that the cases ought to be followed up closely.

DR F E SENEAR I should like to say that probably few of you saw the lesion on the man's left shoulder posteriorly near the scapula because he did not have his shirt off. I think that if you saw that you would not say that the man has a prurigo eruption. He had some definite scaling papules in that location. We have seen the patient only once before, in making rounds, when we were asked to see the woman. We did get a history that she had been taking quinine, but we did not know that she was taking quinacrine. The eruption on the man's shoulder was not typical of lichen planus, but he had a plaque about the size of a dollar, though irregular in outline, in which there were a number of individual papules, most of which had coalesced to form an irregular plaque. I think the histopathologic changes were more characteristic in the man than in the woman.

DR MARCUS R CARO It was surprising that the lesion in the man, which clinically was questionable lichen planus, was histologically characteristic of that disease. The eruption in the wife was clinically typical though histologically less so.

DR LOUIE H WINER, Minneapolis The patch of reticulated pigmentation on the side of the man's face is typical clinically of lichen planus of the eyelids that Dr Michelson described. The histologic section definitely shows lichen planus. I agree with Dr Caro that the histologic section from the wife shows lichen planus. One sees in the microscopic section of her skin essentially an eosinophilic degeneration of epidermal cells, which is mentioned by Montgomery, Kyrle and others as a characteristic of lichen planus.

# METROPOLITAN DERMATOLOGICAL SOCIETY

ROYAL M. MONTGOMERY, M.D., *President*

JAMES LOWRY MILLER, M.D., *Secretary*

Feb 21, 1944

**Eczema**-(Presented for Therapeutic Suggestions) Presented by DR THOMAS N. GRAHAM

F. G., a white man aged 63, was first examined by me on Dec 27, 1943. He complained of an eruption of two weeks' duration involving his legs, thighs and lower part of the trunk. The original patch began on the lateral aspect of the left leg, just above the ankle. It had appeared at a site of trauma resulting from an accident. There was no history of contact to irritants. The patient complained of severe pruritus in some of the lesions.

On examination there are numerous round and irregular erythematous vesicular patches, some of which exude a serous fluid. The patches range in diameter from 2 to 10 cm. The legs show moderate varices.

Urinalysis showed normal conditions, and the Wassermann reaction of the blood was negative.

The eruption at first almost cleared with fractional roentgen ray therapy. This was followed by an exacerbation which did not respond to roentgen radiation. A total of 450 r to each area was given.

Numerous ointments were prescribed, including zinc oxide ointment with phenol, an ointment containing pine tar and one containing ethyl aminobenzoate. The ethyl aminobenzoate ointment was the only preparation which afforded any relief. The patient has not used soap and water on the involved areas but has cleansed them with olive oil. He has been taking starch baths.

Ultraviolet irradiation improved the eruption for a while, but new lesions appeared.

Vitamins have been prescribed as well as calcium lactate tablets. The patient has been on a high vitamin, restricted carbohydrate diet.

## DISCUSSION

DR MAURICE J. COSTELLO: I suggest compresses of solution of aluminum acetate (1:10) and coal tar paste.

DR LESLIE P. BARKER: It is important to keep the patient off his feet. Permanganate baths and tars should be helpful.

DR J. LOWRY MILLER: I suggest that a snug Unna gelatine bandage be applied to the leg and left on for a week. Ten per cent ichthammol ointment bandages on the leg may also give relief if applied so as to give adequate support.

DR LAIRD S. VAN DYCK: This man should be hospitalized. The eruption will not clear unless he is kept off his feet. I should also prescribe potassium permanganate baths and zinc oxide paste with 1 per cent coal tar.

DR THOMAS N. GRAHAM: I have suggested hospitalization to this patient, but he insists that he cannot take any time off from his job. He has already observed a diet of the type suggested, without any improvement. I shall try to persuade him to be hospitalized for a few weeks, and I agree with the discussers who have suggested this measure as essential in effecting a cure.

**Generalized Lichen Spinulosus, Alopecia Cicatricata** Presented by DR LAIRD S. VAN DYCK

A. L., a white man aged 57, in January 1933 first noticed that the skin on his trunk and thighs was

getting rough and spiny. At that time he applied an ointment containing salicylic acid, hydrous wool fat and cold cream, and the spiny lesions gradually disappeared after a few weeks' treatment. Three months ago the eruption recurred on the arms, legs and trunk. The scattered atrophic bald areas in the scalp have been present since childhood. His diet is normally balanced and shows no deficiency in vitamin A.

On examination the trunk and extremities are covered with scattered, discrete, acuminate, follicular, keratotic and spiny lesions. There is no redness of the skin such as one finds in pityriasis rubra pilaris and no hyperkeratosis of the palms and soles. The hair of his scalp is absent in small scattered patches, which show smooth atrophy and no signs of inflammation.

The Wassermann reaction of the blood was negative.

## DISCUSSION

DR J. LOWRY MILLER: The occurrence of these diseases together has been reported in a number of patients. What the connection is between the two I do not know. Vitamin A therapy might be worth trying.

DR MAURICE J. COSTELLO: All the manifestations which the patient presents are related. They may be congenital. I suggest that he be given 300,000 U. S. P. units of vitamin A daily.

DR LAIRD S. VAN DYCK: I first saw this patient eleven years ago, with this same eruption. He states that his skin cleared after he used a salicylic acid ointment and stayed clear until about three months ago.

**Pityriasis Rubra Pilaris** Presented by DR THOMAS N. GRAHAM

J. B., a white woman aged 51, was first examined by me on Jan 22, 1944. She complained of a generalized eruption of three months' duration which at times itched and which at other times was asymptomatic.

On examination there are numerous follicular keratotic lesions on the trunk and the extremities. The palms show decided hyperkeratosis and fissuring. The face presents erythema and scaling.

The Wassermann reaction of the blood was negative. A biopsy has been performed, but a histopathologic study has not yet been made.

Treatment with 200,000 U. S. P. units of vitamin A daily and the application of a keratolytic ointment containing salicylic acid and ammoniated mercury over a period of two weeks have resulted in slight improvement. While under observation some of the hyperkeratotic follicular lesions have become confluent and have produced scaly patches.

## DISCUSSION

DR ROYAL M. MONTGOMERY: I agree with the diagnosis.

DR MAURICE J. COSTELLO: I think this patient has lichen planus of some type, such as lichen planopilaris.

DR J. LOWRY MILLER: I agree with the diagnosis of lichen planus.

DR LESLIE P. BARKER: I think that it is lichen planus.

DR THOMAS N. GRAHAM: When I recently presented this patient at a New York hospital conference she showed a clinical picture much more typical of pityriasis rubra pilaris than she does tonight. At that time the lesions were definitely follicular and keratotic and they did not show the scaling which they do at present. It would be difficult to be sure of this diagnosis tonight, but I believe that the diagnosis as presented is correct.



NOTE—Studies of sections from the biopsy specimen showed them to be consistent with a diagnosis of pityriasis rubra pilaris

### Neurodermatitis Occurring in Mother and Child Simultaneously Presented by DR MAURICE J COSTELLO

A W, a woman aged 49, has had an extremely pigmented, lichenified, pruritic eruption on the flexors of the extremities, the back and neck for the past five years

V W, her daughter, aged 7, has had an extremely pruritic, diffuse, hyperpigmented eruption for the past six years. Her father and his two sisters have suffered from asthma. They have improved with application of coal tar preparations and ultraviolet irradiation

#### DISCUSSION

DR ROYAL M MONTGOMERY In the case of the child I believe the diagnosis is correct. The mother's eruption I believe is an arsenical dermatitis following the treatment of syphilis

DR THOMAS N GRAHAM I agree with the diagnosis as presented

DR LESLIE P BARKER I think that the mother has an arsenical dermatitis. During each of her pregnancies she received arsenical therapy. Could the child have been sensitized to arsenic?

DR J LOWRY MILLER Neurodermatitis is the best clinical diagnosis, but these 2 cases are of especial interest, as they are both probably due to sensitization to arsenic. The mother received arsenical treatment during her pregnancy with this child. This clinical picture is seen frequently enough following administration of arsenic to suggest that as the cause

DR MAURICE J COSTELLO I thought the mother had unusual discoid lesions when I first saw her. I presented these cases because the mother and daughter had similar eruptions running their course at the same time. There is a family history of allergy

### A Case for Diagnosis (Nevus Linearis, Neuroma of Ankle, Melanoma of Right Wrist?) Presented by DR LAIRD S VAN DYCK

M G, a woman aged 24, a secretary, first noticed a brown linear lesion on her right leg about six years ago. Since that time it has extended slightly, but she has never noticed any itching or pain

On examination of the lower third of the right leg there is seen a light brown, slightly raised, linear lesion just above the ankle, extending downward and medially from the lateral aspect of the leg toward the internal malleolus. There is a bluish nodule on the dorsum of the right wrist

Biopsy of a specimen from the medial portion of the lesion of the ankle showed neuroma. A second biopsy from the lateral end of the ankle lesion also showed neuroma

#### DISCUSSION

DR MAURICE J COSTELLO I do not know the diagnosis for the lesion on the leg. The dorsum of the hand however, is the most common site for the blue-black mole. I think that the lesions are not related

DR LAIRD S VAN DYCK This patient was presented at a staff conference of the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital. There was no agreement there as to the diagnosis for the lesion on the ankle

### Riehl's Melanosis Presented by DR LESLIE P BARKER

D D, a Negro housewife aged 39, was first seen on Feb 1, 1944, at which time she gave a history of having a brownish pigmentation on the face for the past six months which followed the use of Noxema for the prevention of sunburn. She applied the ointment before exposure to sunlight and then noticed a patchy pigmentation on the face. She has never had injections of arsenic or bismuth preparations, to her knowledge

Examination shows a mottled macular dark brown pigmentation involving most of the face, except the lateral part

The Wassermann reaction of the blood was negative

#### DISCUSSION

DR THOMAS N GRAHAM One should not call this eruption Riehl's melanosis as this often occurs in persons who handle tar. Is there tar in Noxema? Some ingredient has caused it

DR ROYAL M MONTGOMERY I believe that the pigmentation was caused by the application of Noxema

DR MAURICE J COSTELLO I agree with the diagnosis

DR J LOWRY MILLER I agree with the diagnosis

### Keratosis Plantaris and Radiodermatitis Presented By DR ROYAL M MONTGOMERY

G L, a woman aged 29, from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, states that she has had callosities for fifteen years. She was previously presented before the New York Dermatological Society, on March 24, 1942, by Dr Paul Bechet (ARCH DERMAT & SYPH 46 762 [Nov] 1942) and also before the New York Academy of Medicine, on April 7, 1942, by Dr Max Scheer (ARCH DERMAT & SYPH 46 910 [Dec] 1942)

She is presented because of clinical changes and to show the results of treatment. Between November 1935 and July 1938 she had twenty roentgen ray treatments at a New York hospital (total dose 6,946 r) for callosities on the plantar surface of the feet

On examination the right foot presents an area of hyperkeratosis under the first and second metatarsal heads extending onto the lateral side of the big toe. There are capillary tips varying in size in this keratotic mass. In the surrounding skin are many telangiectatic blood vessels. (These features were not mentioned in the previous presentations.) An area  $\frac{1}{2}$  inch (1.2 cm) in diameter of similar consistency is present over the fifth metatarsal head. These keratotic areas are moderately fixed to the underlying structures

On the left foot similar areas are present. One large area extends under all the metatarsal heads and onto the big toe in an L-shaped manner. The surrounding skin is telangiectatic. These keratotic masses have been thinned by paring

Keratotic masses  $2\frac{1}{2}$  inches (6.4 cm) in diameter were removed from the heels by plastic surgery. The left heel was operated on in January 1942 and the right in November 1943

The patient is presented to show results of treatment. The graft on the left heel has formed several keratotic lesions since the operation. This was predicted when she was presented at the New York Dermatological Society. The right heel was repaired, with good results so far. When seen by me in April 1942, the patient had to use crutches. The keratotic masses were



$\frac{3}{4}$  inch (2 cm) thick. Since then they have been thinned with the aid of salicylic acid and a scalpel. Walking has been facilitated by the use of a foam rubber pad across the front of the foot. She has not used crutches since June 1942 except after the plastic repair on the right heel. The vascular elements in the keratotic lesions have decreased in number.

#### DISCUSSION

DR MAURICE J COSTELLO. Evidently the radiologist treated the lesion with roentgen rays through a large portal. A dermatologist would not do that. I recently saw a patient with callosities similar to these and sent her to a surgeon for a plastic operation. However, I understand these lesions will break down eventually.

DR J LOWRY MILLER. In connection with the recurrence of the verrucous lesions in the area where skin grafting was done, I think this phenomenon is due more to the impaired blood supply than to a recurrence of the disease. I saw a patient recently who had had

began as an itching papule and gradually spread. Considerable pus drained from the surface of the lesion despite the use of many different local remedies. The past history and the family history of the patient were irrelevant.

Examination shows an oval-shaped lesion 8 by 4 inches (20 by 10 cm) on the middle third of the left leg over the shin. The lesion is red, with sharply demarcated serpiginous borders. Scattered throughout the lesion are dime-sized to quarter-sized ulcerations which are fairly superficial and covered with yellow pus. The lesion is not elevated but rather slightly atrophic.

Repeated cultures showed aerobically hemolytic *Staphylococcus aureus* and no anaerobic growth. A biopsy from the lesion showed a necrosis of the deeper layers of the corium and fat surrounded by granulation tissue, with numerous epithelioid cells and a few giant cells. There was perivascular inflammation and thickening. The lesion was, in all probability, infectious granuloma. A urinalysis, blood count, determinations of blood sugar,



A, before treatment, April 14, 1942. Thick keratotic areas are present under the heads of the metatarsal bones and on one heel. B, after treatment, April 14, 1944. The keratotic areas have been thinned by applications of salicylic acid and by shaving. Soft foam rubber pads are used under the anterior part of the feet. The heels show the result of plastic surgical procedures.

a skin graft over a fairly large area on the leg following a chemical burn. Verrucous areas were developing in the graft and around the toes which had not been affected. Roentgen therapy for keratosis plantaris is contraindicated, as the amount necessary for cure is too large to be given with safety over so large an area.

DR ROYAL M MONTGOMERY. The treatment administered has given the patient much relief, and she is able to walk with ease. The affected areas are slightly smaller and not so vascular. The outlook is poor unless she has plastic repair to the anterior plantar surfaces. The results may not be perfect, but the precancerous masses will have been removed.

#### A Case for Diagnosis (Syphilis, Tuberculosis?)

Presented by DR J LOWRY MILLER

D K, an unmarried Greek woman aged 21, was admitted to the Vanderbilt Clinic in September 1943, complaining of an ulceration on the left shin. The lesion

blood cholesterol and basal metabolic rate and roentgenogram of the chest all gave normal results. The Wassermann reaction of the blood and of the spinal fluid was negative. Old tuberculin in a 1:100,000 dilution elicited a negative reaction while a 1:10,000 dilution elicited a strongly positive reaction.

Treatment consisted of eighteen intramuscular injections of 1 gram (0.06 Gm) of mercury salicylate given at weekly intervals and daily local use of 2 per cent gentian violet medicinal.

All ulcerations healed in three months, leaving a thin atrophic scar with a reddish brown pigmentation throughout the entire lesion.

#### DISCUSSION

DR LESLIE P BARKER. I think that this is tertiary syphilis. It looks like it clinically. I suggest treatment with arsenic. Then, too, the Wassermann reaction may become positive.

DR THOMAS N GRAHAM I recall having seen this patient at the Knickerbocker Hospital before she was seen by Dr Miller. At that time she presented punched-out ulcerations in serpiginous configuration which strongly suggested tertiary syphilis. The Wassermann reaction of the blood was negative. The report of a biopsy was indefinite but favored a diagnosis of syphilis. In view of the response to antisyphilitic treatment, I believe that the most probable diagnosis is tertiary syphilis.

DR MAURICE J COSTELLO I do not think that this is cutaneous syphilis. My diagnosis, without being influenced by the history, would be necrobiosis lipoidica.

DR ROYAL M MONTGOMERY I agree with the diagnosis of syphilis.

DR J LOWRY MILLER I am not convinced that this patient has syphilis. There is a suggestion of yellowness in the lesion, but histologic examination in no way suggested necrobiosis lipoidica. The response to injections of a bismuth preparation was dramatic. There is no other clinical or laboratory evidence of syphilis except the response to therapy and the suggestive histologic picture.

**Dermatitis Medicamentosa (Arsenic, Phenolphthalein?)** Presented by DR J LOWRY MILLER

L S, aged 34, a Negro housewife, was admitted to Vanderbilt Clinic on Feb 16, 1944 complaining of itching lesions scattered over most of the body but particularly in the intertriginous areas. The patient said she had been well until a routine Wassermann test was reported as eliciting a 4 plus reaction in 1942. She began to take antisyphilitic treatment at this time. While receiving "arm injections" in June 1943, she began to have an itching eruption which appeared first in the axillas and soon spread to many areas. She was taking Ex-Lax at the time. When she stopped taking it, her eruption continued. The "arm injections" were stopped in July 1943, but the "hip" injections were continued until her admission to the clinic.

Examination shows that behind the ears, in the axillas and groins and on the abdomen, neck and arms there are deeply brownish black, pigmented lichenified areas. The nails and hair appear normal. There is no bismuth line around the gums.

No laboratory reports have been received as yet.

#### DISCUSSION

DR MAURICE J COSTELLO I do not believe these lesions are caused by Ex-Lax. Lesions caused by phenolphthalein are seldom pruritic. I think that the dermatitis is due to arsenphenamine.

DR LESLIE P BARKER I agree with Dr Costello. It is known that patients retain arsenic long after treatment.

DR LAIRD S VAN DYCK I agree with the previous speakers. I believe that arsenic plays a part in a good many conditions in which its influence is not yet recognized.

DR J LOWRY MILLER The clinical features are those generally found as a result of arsenic, not of sensitivity to phenolphthalein.

**Glossitis Due to Vitamin Deficiency** Presented by DR MAURICE J COSTELLO

M K, a woman aged 61 born in Germany, has had a sore tongue for the past twenty years. In addition to this she has had an eruption on the right palm and

left sole for three years. She has also noticed the development of a robin's egg-sized node in the left upper cervical region. The lesions on the tongue consist of glossy areas with some fissuring and sharp margination. Since the administration of liver extract began a week ago, the burning and soreness of the tongue have improved and the affected areas have assumed a healthier appearance.

#### DISCUSSION

DR ROYAL M MONTGOMERY I was interested in the lesion on the neck. I think it warrants investigation pathologically. It may be malignant.

DR THOMAS N GRAHAM I believe that this patient does not have cancer. She has an enlarged lymph node below the right side of her jaw as well as the one noted below the left side of her jaw. This bilateral adenopathy does not favor a diagnosis of epithelioma.

### BROOKLYN DERMATOLOGICAL SOCIETY

C THOMAS CHIARAMONTE, M D, *President*

SEYMOUR H SILVERS, M D, *Secretary*

*Feb 21, 1944*

**Herpes Gestationis** Presented by DR NATHAN PENSKY

B L, a Negro woman, aged 31, gives a history of having been pregnant ten times. She is now in her eighth month of pregnancy. Her first three children were born at term and are living and well. She aborted her fourth and fifth pregnancies at three and at two and one-half months respectively. Her sixth pregnancy was uneventful, and her child was born at term and is living and well. She aborted her seventh and eighth pregnancies at three months. Her ninth pregnancy was normal, and the child was born at term. During her sixth, ninth and tenth pregnancies an eruption similar to the present one developed. During her sixth pregnancy the eruption started at the fourth month, disappearing three weeks after delivery. During her ninth pregnancy the eruption developed at the eighth month and disappeared one week after delivery. In the course of the tenth pregnancy the eruption developed at the seventh month and is now present.

The patient presents many crusted areas, especially about the inner surface of the left breast, in the left groin and on the back. In addition, there are scattered clusters of bullae of various sizes, particularly noticeable in the left groin. There are many pigmented areas about the back and abdomen. Many of the crusted lesions appear to have been recently dried bullae. The patient has a cystic adenoma of the thyroid gland which has been present for the past seven years.

#### DISCUSSION

DR NATHAN PENSKY An interesting feature of this case is the benign outcome of the pregnancies during which dermatitis is present. The lesions disappeared rapidly on termination of pregnancy and the children survive. During the periods ending in abortion the patient has never had dermatitis.

DR DAVID M. DAVIDSON Dermatitis gestationis may have various clinical pictures. The most common ones are those of erythema multiforme and dermatitis herpetiformis. In the case presented tonight the eruption consists of scattered herpes-like lesions, therefore the name herpes gestationis is appropriate.

#### Xeroderma Pigmentosum with Malignant Changes Presented by DR SEYMOUR H. SILVERS

This boy was presented about two years ago (ARCH DERMAT & SYPH 46 613 [Oct] 1942)

On the right lower angle of the nose and cheek there is a pea-sized red ulcerated, crusted lesion, with

a raised, pale border. A similar lentil-sized lesion is present on the middle of the chin.

#### DISCUSSION

DR SEYMOUR H. SILVERS The parents of this boy are first cousins. He is now 15 years of age. The reason for presentation at this time is to discuss the question of treatment. The diagnosis was obvious when he was first presented, two years ago, but recently for the first time I noticed changes which I consider to be malignant. The questions now are: What is the best treatment, in view of his age, and what is the possibility of his survival?

## News and Comment

### COURSE IN TROPICAL DERMATOLOGY

Under the direction of Dr. Fernando Latapi, professor of dermatology, Universidad Nacional de Mexico, and with the cooperation of the Secretaria de Salubridad, a practical course in English on dermatology of the American tropics will be given in Mexico City, Aug. 6 to 18, 1945. Presentations of cases and lectures will be held at the Hospital General, where there is abundant material, and at other institutions, and laboratory sessions will be held at the Institute of Tropical Diseases, the director of which is Dr. Jose Zozaya. Attendance is limited to approximately thirty qualified American dermatologists. There will be no fee for the course.

The general outline of the course, subject to change, is as follows:

Dr. Gonzalez Herrejon—Mal del pinto

Dr. Manuel Martinez Bacz—Onchocercosis

Dr. Gonzalez Ochoa—Mycoses

Dr. Fernando Latapi—Leprosy, Observations on Variations of the Common Diseases of the Skin

Other clinical subjects, such as cutaneous avitaminosis in the tropics, cutaneous pictures of typhus, medical

entomology as related to dermatology and chemical control of insects, will also be given. At the Institute of Tropical Medicine the parasites and the pathology of parasitic diseases will be studied in detail, in addition to material on leishmaniasis and verruga peruana.

For those who are interested, opportunities may be given for small groups to do field surveys in leprosy, mal del pinto and onchocercosis.

Applications for the course should be sent immediately to Dr. Leon Goldman, 733 Carver Tower, Cincinnati 2, Ohio.

### RESUMPTION OF PUBLICATION OF THE JOURNAL OF INVESTIGATIVE DERMATOLOGY

The Society for Investigative Dermatology announces the resumption of publication of their periodical the *Journal of Investigative Dermatology*, which temporarily suspended publication in 1942 on account of war conditions. The first number of volume 6 appeared in February. It will be issued bimonthly, one volume a year, at \$6 the volume, by The Williams & Wilkins Company, Baltimore 2, Md.

## ECTHYMA CONTAGIOSUM IN MAN

DATA CONCERNING ITS INCIDENCE IN SEVERAL WESTERN STATES,  
REPORT OF A CASE

I L Y L E B K I N G E R Y, M D, A N D J O Y L E D A H L, M D

P O R T L A N D, O R E

In 1923, Aynaud<sup>1</sup> reported the results of his studies on ecthyma contagiosum. In this report he described experimental procedures definitely identifying the disease as due to a filtrable virus and apparently peculiar to sheep and goats. Following this early work, the results of similar studies have been published by Glover,<sup>2</sup> Boughton and Hardy,<sup>3</sup> Oppermann and Stumpke,<sup>4</sup> Marsh and Tunncliffe<sup>5</sup> and others. As a result of these investigations, there is now available a rather complete and detailed knowledge of the disease as it exists in the animals studied. This information may be summarized somewhat as follows:

- (a) The disease is due to a specific filtrable virus
- (b) It is apparently peculiar to sheep, goats and man
- (c) It is known to exist throughout most of the wool-producing areas of the world
- (d) Where preventive measures are not employed, it may be characterized by a high annual incidence rate with impressive mortality in susceptible animals
- (e) It may, therefore, at times assume economic aspects of considerable importance
- (f) And, finally, it can be efficiently prevented by the use of a specific vaccine

From the University of Oregon Medical School, Department of Dermatology and Syphilology

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 21, 1944

1 Aynaud, M. La stomatite pustuleuse des ovins (chancre du mouton), Ann Inst Pasteur **37** 498 (May) 1923

2 Glover, R. E. Contagious Pustular Dermatitis of Sheep, J Comp Path & Therap **41** 316 (Dec) 1928

3 Boughton, I. B., and Hardy, W. T. Contagious Ecthyma (Sore Mouth) of Sheep and Goats, J Am Vet M A **85** 150 (Aug) 1934

4 Oppermann, T., and Stumpke, G. Der Lippen- und (Ecthyma contagiosum) der Schafe und seine Übertragbarkeit auf den Menschen, Arch f Dermat u Syph **176** 337, 1937

5 Marsh, H., and Tunncliffe, E. A. Stomatitis in Young Lambs Involving Actinomyces Necrophorus and the Virus of Contagious Ecthyma, J Am Vet M A **91** 600 (Nov) 1937

In spite of the established frequency and world-wide distribution of the disease in animals, there is available relatively limited information concerning its occurrence in man. A few isolated reports have been published from widely separated localities. These include the publications by Peterkin<sup>6</sup> from England, by Orbaneja<sup>7</sup> and Robert<sup>8</sup> from France, by Oppermann and Stumpke<sup>4</sup> from Germany, and by Schoch<sup>8</sup> and Nomland<sup>9</sup> in this country. Dermatologic texts devote but little space to a description of the manifestations of the infection in man. One is more or less entitled to assume, therefore, either that the human disease is one of extreme rarity or that the general medical profession is unfamiliar with this particular clinical picture. The present study was undertaken for the purpose of recording the findings in an additional case of human infection in a locality from which it had not been previously reported, to present the total clinical picture as found by various previous observers, and to establish the fact that at least in this country it is a disease of greater frequency and wider distribution than available information has led us to believe.

## REPORT OF CASE

*History*—Mr. W. H., aged 34, a farm laborer, was referred to us for diagnosis and advice on Jan. 6, 1944. His history revealed that during the three weeks preceding the time of consultation he had been engaged in treating a band of sheep for so-called "fluke disease." This treatment necessitated the forcible opening of the sheep's mouth and the insertion of a large capsule in a manner that would compel the animal to swallow the medication. In the process his hands and

6 Peterkin, G. A. G. The Occurrence in Humans of Contagious Pustular Dermatitis of Sheep ("Orf"), Brit J Dermat **49** 492 (Nov) 1937

7 Robert, P., and Orbaneja, G. Trois cas de granulomes angiopapillomateux eruptifs infectieux, Ann de dermat et syph **8** 45 (Jan) 1937

8 Schoch, A. Sheep Pox Infection in Man, Arch Dermat & Syph **39** 1040 (June) 1939

9 Nomland, R. Human Infection with Ecthyma Contagiosum, a Virus Disorder of Sheep, Arch Dermat & Syph **42** 878 (Nov) 1940



Fig 1—Lesions as they occur in an infected animal



Fig 2—Note papulovesicular and papular pustular lesions, some with umbilication



Fig 3—Portion of section showing hemorrhagic vesicle. The biopsy report and the photomicrograph were secured from Professor Warren C Hunter, of the Department of Pathology, University of Oregon Medical School

fingers were frequently traumatized by the sharp edges of the sheep's teeth. He stated that a large percentage of the animals had "pustular growths and scabs" on their lips (fig 1).

Several days after beginning this work the lesions for which he consulted us began to appear. The patient further described exactly similar lesions on the hands and fingers of 2 of his co-workers. His general medical history was negative.

*Examination*—The general physical examination and ordinary laboratory work revealed nothing noteworthy. The dermatologic examination revealed three lesions on the right thumb and scattered similar lesions on the fingers of each hand. Each lesion was situated on a circular erythematous base averaging from 1 to approximately 2 cm in diameter. The lesions consisted of rather firm papules, papulovesicular and pustular lesions with some suggesting umbilication and

masses of blood pigment, clumps of bacteria and nuclei of what could well be disintegrated leukocytes were at times caught. The cavity was filled with intact erythrocytes, together with a few granulocytes and lymphocytes. The rete mucosum was intact except for the cells that bordered immediately on the blood-filled cyst. Here the more exposed cells were becoming detached and showed evidences of necrosis. The corium was the seat of many dilated vascular channels, most of which were quite devoid of blood. These could be either lymphatics or blood capillaries. Some areas of the corium contained leukocytes in moderate numbers. Some of these were granulocytes but the majority appeared to be lymphocytes. In addition to leukocytes, there were many other cells in the corium. These were rather pale, ovoid to spindle shaped, and looked not unlike the endothelial cells that lined the vascular channels. Their exact nature is unknown but they

TABLE 1—Reported Cases of Human Infection

Reported by		Source of Infection	Incubation Period	Type of Lesion	Distribution	Accompanying Symptoms	Duration
Peterkin	1	Contact with animal	Not given	Ulcer	Finger	None	3 weeks
	2	Contact with animal	Not given	Nodule, umbilicated bleb	Hand	Not given	3+ weeks
	3	?	5 days	Umbilicated pustule	Finger	Pain	Not given
	4	Contact with animal	Several days	Umbilicated pustule	Eye lid	Pruritus	4+ weeks
	5	Contact with animal	Not given	Umbilicated pustules	Thumb	Not given	2 weeks
Robert and Orbaneja	1	Contact with animal	Not given	Pustular, vesicular, papillomatous	Nose and temporal region	Adenopathy	Electro coagulation
	2	Contact with animal	Not given	Pustular, vesicular, papillomatous	Nose	Adenopathy	Electro coagulation
Oppermann and Stumple	1	Needle puncture	Apparently blood stream infection with fever and joint pains, blood injected into sheep produced typical lesions				
	2	Contact with animal	Several days	Vesicles, pustules, ulceration	Hand	Not given	Not given
	3	Contact with animal	Not given	Small inflammatory macules and vesicles	Hand and neck	Inflammation, swelling itching	Not given
Schoeh		Contact with animal	3 days	Pustules	Wrist	Adenopathy	3 weeks
Nomland	1	Contact with vaccine	4 days	Bullae, vesicles	Fingers	Pain, redness	3 weeks
	2	Contact with animal	7 days	Vesicles, pustules	Fingers	Swelling, inflammation	Not given
Authors' case		Contact with animal	Days	Papular, vesicular, pustular	Fingers	Mild pain and itching	3-4 weeks

hemorrhage. There was local heat, and the patient described mild accompanying subjective symptoms. There was no adenitis and no mention made of constitutional manifestations. Because of the interesting clinical picture and history, Dr. Thomas Saunders was asked to see the case with us and assisted in its identification. As stated by Nomland,<sup>9</sup> the diagnosis is made by exclusion. The condition bears no resemblance to the ordinary vesicular and pustular diseases of the hands. At the same time, a recent vaccination, vaccinia and milkers' nodules can be readily excluded. Photographs (fig 2) were made and biopsy material taken but we were not given time for further laboratory study. A week or so later the patient's physician informed us that the lesions had completely healed under applications of a mild mercurial cream.

*Pathologic Report*—Microscopically (fig 3) there was found to be splitting of the epidermis through the stratum granulosum leaving an outer wall consisting of partially and fully keratinized epithelium in which

are presumed to be young fibrous connective tissue cells. No inclusion bodies were made out in the epithelial cells of sections stained in the usual manner with hematoxylin and eosin.

*Pathologic Diagnosis*—The diagnosis was intracutaneous hemorrhagic vesicle with focal subacute inflammation.

Ordinarily, the total clinical picture of a given disease entity is most accurately represented by a gradual accumulation of the observations of several individual investigators. With this in mind, a compilation of the findings included in previous reports, together with our own, is shown in table 1. From the information thus tabulated certain general statements may be made regarding the characteristics of the disease as recorded thus far.



They are as follows

1 Human infection is apparently acquired by actual contact with infected animals or laboratory material There are no proved cases of infection from working in stables or from contact with vegetation in which the animals graze

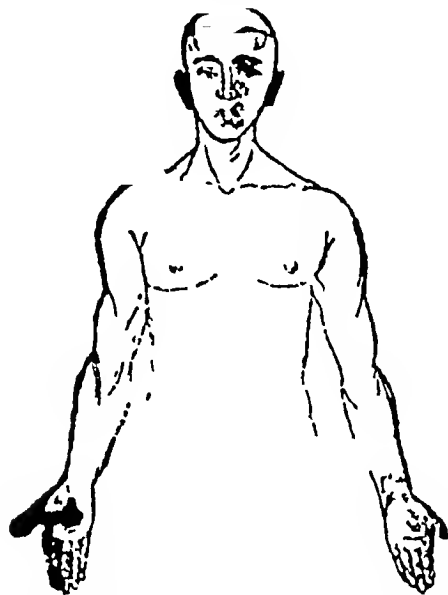


Fig 4—Stippled areas showing distribution of lesions in reported cases

The occasional occurrence on parts of the face could well result from contact with material carried by the fingers or nails

5 Accompanying symptoms are not striking They may be completely absent or may include mild swelling, pain and adenitis

6 The disease may well be self limited In all reported cases the lesions have disappeared in a matter of weeks under the mildest types of local symptomatic therapy

7 Finally, while the information in table 1 emphasizes the limited number of cases of human infection on record, the widely separated sources of these reports suggest a possible incidence and distribution not ordinarily included in the conception of the disease as it is now known

In order to obtain further information relative to the frequency and geographic distribution of the disease in this country questionnaires were sent to various agricultural colleges and experimental stations The states chosen represent an area producing approximately 60 per cent of the country's total wool output It was presumed that information obtained from these sources might be accepted as applying with reasonable accuracy to sheep-growing sections in general

TABLE 2<sup>10</sup>—Observations on Human Infection by State Laboratories and Experiment Stations

State	Frequency	Source of Infection	Type of Lesion	Distribution	Accompanying Symptoms	Duration	Immunity
Washington	Occasional	Contact with animal	Not given	Hands	Not given	Several weeks	Not given
Oregon	Seen occasionally among handlers	Contact with animal	Not given	Hands	Pain	Not given	Not given
California	Seen occasionally among handlers	Contact with animal	Pustules	Fingers	Pain, swelling, inflammation	Several days	Not given
Idaho	Known to occur	Contact with animal	Not given	Not given	Not given	Not given	For life
Montana	Occasional among handlers	Contact with animal	Vesicles, pustules	Hands	Not given	Not given	Not given
Wyoming	Occasional among handlers	Contact with animal	Not given	Not given	Not given	Not given	Not given
Texas	Fairly common	Infected animals, laboratory material	Vesicles, pustules, ulcers	Fingers, hands lips	Inflammation, itching	10 days	Presumably for life

2 The incubation period is short, apparently varying from a few days to one week

3 The evolution of the disease and lesional types are consistent The first manifestation is usually noted as one or more inflammatory elevations with rapid development of vesicles or bullae which may, or may not, show hemorrhage There is a tendency for some lesions to develop umbilication, and the contents often become purulent Occasional ulceration occurs, and in some cases the lesions have become papilomatous

4 The sites of predilection, as would be expected, include the fingers, hands and wrists

Obviously, the data thus obtained represent the observations of persons most interested in the disease as it occurs in animals At the same time, it is this group of investigators who have contributed most to our knowledge of the disease and by reason of their activities have been in constant touch with large numbers of herders and employees in whom one would expect the greatest incidence of infection Their observations are recorded in table 2<sup>10</sup> and permit certain

10 Personal communications to the authors from E E Wegner, State College of Washington, Pullman Wash , J N Shaw, Oregon State College, Corvallis, Ore , J W Britton, College of Agriculture, Davis,

(Footnote continued on next page)

further generalizations concerning human infection. They are as follows:

1 Apparently, one may assume the disease to be endemic in many localities, observations varying from "occasional" to "fairly common" in the states contacted.

2 Complete unanimity of opinion exists concerning the mode of transmission, i. e., contact with infected animals or with laboratory material.

3 The types of lesions seen, their sites of election, the accompanying symptoms and their duration, when observations were made, correspond to those noted in table 1.

4 Finally, one of the observers<sup>2</sup> who has contributed largely to the perfection of an effective vaccine suggests the development of a lasting immunity following one attack.

#### SUMMARY

A summation of the foregoing data would seem to permit a reasonably complete description of human ecthyma contagiosum and to emphasize certain characteristics of the disease not stressed in previous reports. Primarily, clinical and experimental observations have definitely established the cause and methods of acquisition. Further, the eruptive manifestations and accompanying symptoms are fairly consistent and run true to type. The disease may occur on the face as well as on the fingers, hands and wrists. Individual immunity after one attack is a distinct possibility. Finally, while the lack of disabling symptoms and ease of curability make for a professional interest that is largely academic, the disease should be recognized as a dermatosis occurring with a greater frequency and wider geographic distribution than previous investigations have led one to believe.

#### ABSTRACT OF DISCUSSION

DR RUBEN NOMLAND, Iowa City. I wish to express my appreciation of the presentation of the paper on this disease which is apparently rare.

People who live in rural areas have eruptions that are unfamiliar to the urban dermatologist, and most of these have escaped expert reporting. Ecthyma contagiosum is one of these diseases. Dr Kingery and Dr Dahl have definitely shown that in sheep-raising areas this disease is rather common.

I believe that as time goes on more and more cases will be recognized. The clinical description that he has given is comparable to descriptions of cases reported in the literature, to Dr Schoch's case and to the 2 that I saw.

Calif., Glenn C. Holm, University of Idaho, Moscow, Idaho. Hadleigh Marsh Agricultural Experiment Station Bozeman Mont. A. M. Lee, University of Wyoming Laramie Wyo. I. B. Boughton Agricultural College of Texas, Sonora, Texas.

The clinical lesion has a great resemblance to a smallpox vaccination with small pustular formation and finally, a rather large, umbilicated pustule with a surrounding zone of great inflammation, drying up and leaving a necrotic crust. This is, as nearly as I can tell, the course of most of the lesions. Occasionally papillomatous lesions are seen.

I think there is a great similarity between this disease and milkers' nodules, another virus disorder of animals which, also, in the United States has been only briefly described. Milkers' nodules, as far as I know, have been described in only one paper in the American literature, and still milkers' nodules are rather common in rural communities. Again, it is usually a trifling infection, with a self-limited course, and does not come to the attention of the expert who might be interested in reporting it. However, one sees milkers' nodules rather frequently in rural Iowa. In talking to observing general practitioners in rural areas, one learns that the disease is rather common and seldom requires expert care.

Ecthyma contagiosum is in the same category—a fairly common, minor, self-limited disease which occurs in those areas in which sheep are bred.

DR JAMES W. JORDON, Buffalo. We have had 1 case of this condition in Buffalo. The disease probably did not originate in the state of New York. It occurred in a trainman who handled sheep that were coming on a train from the West. About five days later he had an eruption similar to that described in this paper.

Recently 3 cases of milkers' nodes were seen. As far as I know, we have never had a case of this infection in Buffalo before. All of these came from one section, around East Aurora, which is a suburb of Buffalo. All the patients were milkers working on dairy farms. All reported that the cattle they worked with had some sort of eruption on the udders. The infection usually started in an area of broken skin such as a scratch or some other traumatic lesion. There is a decided difference clinically between the two diseases. Ecthyma contagiosum is a bullous or pustular eruption and milkers' nodes are red, raised vesicular nodules that resemble pyogenic granulomas except that the surfaces of the nodules do not become eroded. They usually start with a single lesion and about this two or three other nodules appear in close proximity. Shortly after the appearance of the nodules on the skin, the regional lymph nodes enlarge. The nodes are rather large, varying in size from that of a hickory nut to that of a walnut. They are firm, not attached to the overlying skin or the underlying tissues. This disease is self limited and tends to clear up of its own accord in six to ten months.

DR JOSEPH V. KLAUDER, Philadelphia. An interesting aspect of this disease is the possible use of vaccination to extend the therapeutics of diseases of the skin caused by viruses and those presumably caused by viruses, in much the same way as vaccination for smallpox is used.

Does Dr Kingery think that vaccination for this disease would be any more hazardous than vaccination for smallpox?

DR BEDFORD SHELMIER, Dallas. An eruption of the hands the clinical appearance of which is identical with that of human ecthyma contagiosum is by no means rare in my practice. Dr Jordon has ably described the lesions when he stated they resemble multiple smallpox vaccinations. In most instances persons affected

with the disease gave a history of milking cows and invariably the cows were said to have had sores on the udders. In at least 2 instances I called in veterinarians who diagnosed the eruption on the cow udders as "cowpox." Therefore, I simply dismissed the diagnosis as cowpox contracted from handling infected udders of cows. Since many of the patients also handled sheep it is possible that the disease was contracted from these animals.

I had the privilege of seeing the case of sheep-pox described by Schoch. There was absolutely no doubt that this man had contracted his infection from sheep. The appearance of the eruption and its clinical benign course were identical with those of the eruption I had seen so frequently following the milking of cows with infected udders. My impression is that sheep-pox and cowpox are clinically identical in man.

DR SAMUEL AYRES JR, Los Angeles. I would like to have Dr Kingery comment on the differentiation between ecthyma contagiosum, which apparently is a distinct entity, and the disease that I think every one is familiar with and which is obviously common, just plain ecthyma. I personally have never seen one of the cases described here, and I think there might be confusion in some minds unless some differentiation was brought out.

DR LYLE B KINGERY, Portland, Ore. Mr Chairman, your question concerning vaccination has been satisfactorily answered by the research work carried

on at the various experiment stations. That is, inasmuch as the vaccine is prepared from material from actual lesions, then used as a preventive in noninfected animals, one may assume its use is attended by no risk. Is that what you had in mind?

DR JOSEPH V KLAUDER, Philadelphia. Yes.

DR LYLE B KINGERY. Dr Shelmire's question, I believe, is answered by some of the correspondence I had with the head of the department of veterinary medicine at our own state university. In my first letter I referred to the disease as "cowpox" and was immediately put in my proper place by being told that bacteriologically and clinically the two diseases were distinct entities, having no relationship. Furthermore, in the case we have reported there was no history of contact with cattle.

Dr Ayres has suggested a possible clinical similarity between ecthyma contagiosum and ordinary ecthyma. If one were to see examples of these two diseases at the same time the complete dissimilarity would be obvious. The former begins as an inflammatory papule on which there is rapidly superimposed a hemorrhagic vesicle or bulla, this gradually becoming secondarily infected and frequently showing central umbilication. The latter begins as a pustule and practically always develops into a crusted pyogenic ulcer. In addition, the two diseases differ as to distribution of lesions, history of exposure and duration.

In closing, I want to express my appreciation of this discussion.

Photographs by Marsh and Tunnichiff

# RECURRENT, RESISTANT VESICULAR ERUPTION OF THE HANDS

J HARPER BLAISDELL, M D, AND JACOB H SWARTZ, M D

BOSTON

The purpose of this paper is to call attention to a chronic, recurrent, resistant vesicular eruption of the palms and fingers that is being seen with increasing frequency and that has certain characteristics that identify it as a definite entity. One and two-tenths per cent of cases seen in our private practice belong in this group.

The predisposing factor in the appearance of this disease is chronic irritation of the affected parts either through occupation or from overstimulating treatment of a simple dermatitis. The majority of cases observed appear in those exposed to hazardous occupations, such as machine operators, porters and bakers. Housewives, with their exposure to soap and hot water in the washing of dishes and clothes, to wide extremes of heat and cold in the kitchen and to house dust, are frequently victims of this disease. Its occurrence in the protected office worker is much rarer, and the eruption in these cases is usually limited to much smaller areas than in other patients. The housewife and office worker often give a history of a duration extending as long as ten years, the attacks coming on several times a year. The persistent use of vigorous and stimulating treatment for simple inflammations of the palms and fingers predisposes to the disease in persons otherwise not subject to it.

The disease occurs on the sides of the fingers, on the palmar aspects of the hands and fingers and in the interspace webbing. The invasion of the backs of the hands or the knuckles occurs only as a secondary spread of a dermatitis from the interspaces. The feet are uninvolved. In a majority of the cases the patient is of the nervous type, with active sweating to the extent of drops of perspiration being present during examination. The skin is often habitually cold and clammy. The unilateral or bilateral character of the disease is entirely dependent on the extent of the initial dermatitis. It is noncontagious.

The primary lesion is a vesicle, varying in size from that of a pinhead to that of a small split pea. It is pearly and translucent and appears on the surface of the skin without producing any trace

of surrounding inflammation. It may occur in small clusters 0.6 to 0.12 cm in diameter, each of which contains pearly vesicles of varying size. The secondary lesion is a scale, the size of which depends on the size of the vesicle.

The clinical history is frequently one of an obvious and adequately explained industrial dermatitis of the hands, which through lack of attention or overtreatment has persisted for several weeks. As the frank signs of the dermatitis subside, the pearly vesicles appear along the edges of the dermatitis, and on occasion in the more or less normal skin adjacent to the outbreak. If secondary infection occurs, the surface of the skin becomes oozing, purulent and crusting, the primary vesicles are masked by this complication. Overstimulating treatment produces the signs of typical acute dermatitis.

With simple drying, soothing treatment the vesicles dry and the skin desquamates. If the vesicles have appeared at about the same time over a period of two or three days, the process of involution results in a relatively normal-appearing skin at the end of ten to fourteen days. If the attack is severe and prolonged, vesicles in all stages of progress appear at the same time.

This disease consists of a recurring series of attacks. In many patients these occur at regular intervals, the most frequent period being every twenty-six to twenty-eight days. At times the interval is as short as eighteen days. So far as can be determined there is no relation to any event such as menstruation. An observing patient can frequently predict the coming of a new attack by the burning and itching of the affected parts twelve to twenty-four hours before the new vesicles appear.

The course of the disease is extremely variable in length. It may disappear after a few months, but often lasts for a year and occasionally as long as two or three years in spite of any treatment of which we are aware.

In the industrial worker protection from the original hazard or a change in occupation may obviate the element of dermatitis, but it has no influence on the recurring vesiculation. There is no seasonal variation and extreme cold or heat has no influence on its course other than the pro-

Read at the Sixty-Fifth Annual Meeting of the American Dermatological Association, Inc., Chicago, June 20, 1944.

duction of a complicating element of secondary dermatitis

Treatment is symptomatic and completely unsatisfactory. Soothing, drying and mildly antiseptic treatment controls the presenting dermatitis and its possible secondary infection without trouble. For this purpose warm soaks of boric acid or of potassium permanganate in solutions of 1:5,000 have proved satisfactory. An exudative dermatitis yields to a 5 to 10 per cent crude coal tar ointment. So far in our experience, nothing has a specific influence on the recurring vesiculation. Use of roentgen and ultraviolet radiation gives temporary relief and hastens the involution of the given attack of vesiculation, but neither is curative. More recently we have used applications of aluminum chloride or hydrosol, and the resulting decrease of the excessive sweating seen in many cases seems promising, but this therapy has not been in use long enough to warrant evaluation.

In the cases studied direct microscopic examination of the roofs of the vesicles has not revealed fungus. The cutaneous scales planted on Sabouraud's medium and grown at room temperature have yielded no pathogenic fungous growth. Some scales yielded *Staphylococcus albus*, but the ratio was the same as that of normal scales of skin planted under the same conditions. A few scales showed a more lucrative growth.

The following cases serve to illustrate the clinical entity discussed.

#### REPORT OF CASES

**CASE 1**—Mrs. D, a 24 year old housewife, was first seen on Aug. 19, 1943, at which time there had been an eruption on her hands for four years. The eruption appeared during her last year in college coincidentally with a course in chemistry and became worse during the first two years of her married life. It appeared three or four times each year for periods of several weeks. During the ten months previous to the initial visit the outbreak had been continuous and worse than at any previous time. This period coincided with the birth of a baby, its daily bathing, washing of diapers and complete care of the home.

A characteristic eruption involved both palms and several fingers of each hand. Repeated direct microscopic examinations and cultural studies of the roofs of the vesicles and the scales by one of us (J. H. S.) did not reveal fungus.

Treatment consisted of use of potassium permanganate soaks in dilutions of 1:5,000, weekly exposures to ultraviolet rays and the application of boric acid ointment. Aluminum chloride in strengths of 10 to 20 per cent was used to curb a moderate hyperhidrosis of the palms that became evident as the dermatitis subsided. Under this regimen the intensity of the vesicular outbreaks became progressively less until apparent recovery took place in the spring of 1944.

The recurring vesicular outbreaks appeared with considerable regularity, as the following dates show: September 4, October 1 and 29, November 30, January 3

and 29, February 28 and March 27. The last attack, which consisted of not more than ten vesicles, followed a week of spring cleaning with considerable washing.

**CASE 2**—Mr. B, a 30 year old meat order clerk, was first seen on Aug. 28, 1942. He worked in a packing plant and handled raw, damp meat all day in a refrigerator room with the temperature in the fifties. He washed his hands frequently with soap powder and cold water. A characteristic eruption was confined to the ring and middle fingers and the forefinger of the right hand throughout the ensuing year. The original outbreak, which had started two months previously and was accompanied by secondary infection, responded to treatment sufficiently for the patient to return to his work after one month. During the next four months the dermatitis waxed and waned, and he treated the outbreaks himself.

In January 1943, the patient gave up handling meat and got a job as an elevator man, using gloves and sparing his right hand as much as possible. Treatment was renewed on Feb. 11, 1943, and after the obscuring dermatitis was quieted, definite vesicular outbreaks appeared on the following dates: March 20, April 26, May 30, June 19 and July 10. He was discharged on August 16 with the skin quite well and with no outbreak during the first part of August. The treatment was essentially the same as that used in case 1.

Examinations (by J. H. S.) did not reveal fungi, and biopsy of a lesion taken from the ring finger showed hyperkeratosis, parakeratosis and some edema of the prickle cell layer. The capillaries of the papillary layer were dilated and surrounded by an inflammatory infiltration, chiefly round cells. A similar infiltration was present about some of the sweat ducts.

#### COMMENT

This clinical entity has been given many names, such as dermatophytosis, *id*, bacterial infection, eczema due to food idiosyncrasies and occupational dermatitis. However, the fact that mycologic studies repeatedly give negative results, both by direct microscopic examination and by culture, does not substantiate the diagnosis of fungous infection. The usual absence of an active focus of fungous infection militates against the possibility of an "*id*." Elimination of suspected foods has produced no beneficial results. Absence from work or a change in occupation does not prevent relapses.

What is this disease? The answer at present can only be speculative. We believe that it is due to an endogenous rather than an exogenous factor, which is set to work when there is lowered resistance of the tissue caused by a severe dermatitis or by continuous or repeated irritation. This endogenous factor may be a toxin, circulating in the blood, set free by severe or continuous damage to the skin. This substance may act on the capillaries or sweat ducts in that area, causing a disturbance in their function and inflammation. The characteristic recurrence in cycles is contradictory to the theory of direct bacterial invasion of a tissue that has developed a lowered resistance as a result of a preceding

dermatitis It is not, however, contradictory to a possible virus infection, since other infections caused by a virus, such as recurrent herpes simplex, may be recurrent and periodic

Further histopathologic studies of the sweat ducts in the involved areas are being made Attempts at reproducing the disease in healthy areas by inoculation with the contents of the vesicles are also being carried out, and the results will be included in a later report

The strongest competitor of this recurrent pearly dermatitis is the currently ignored disease of pompholyx, whose clinical characteristics are closely parallel, but the etiologic sources of the two diseases are completely different Knowles, Corson and Decker<sup>1</sup> say "It is probable that pompholyx is due to absorption of toxins from diseased areas, among them being dermatophytosis The tonsils are very often responsible, as are teeth, sinuses, appendix and other septic foci This would mean hematogenous transmission" Ormsby and Montgomery<sup>2</sup> say "It [pompholyx] is said to occur in persons of nervous temperament and in those who are in a depressed mental state ascribed to worry and overwork It is considered by most observers to be a neurosis, by some to be of toxic origin, the toxin being produced in the gastrointestinal anal"

Nowhere is it suggested that pompholyx may be a sequela of chronic irritation sustained in either industrial or private life On the other hand, in a carefully appraised case, White<sup>3</sup> specifically rules out pompholyx as having any causal relation to industrial dermatitis He writes as follows

The diagnosis was given of "trade eczema" in a man working at a "jug" in which he was using a series of different substantive dyes As the symptoms lasted many months further enquiry elicited the following facts The patient was eventually discovered to have a typical pompholyx (Tilbury Fox's "dysidrosis") unsuspected and therefore untreated by the medical attendant who gave the certificate The rash continued to erupt periodically months after the man left his work Before the man left work the author explained to him that, working or playing, the rash was liable to recur During a two and one-half months' holiday at home and after he returned to a dry and wholesome job, the eruption returned at intervals on his fingers This is the usual custom or habit of cheiropompholyx, a not very common complaint In this case the breaking out was independent of his work It was the result of an internal toxin or irritant at present unexplainable, causing inflammation on these parts After the cuticle

has become broken by disease, it would have been aggravated or made worse by his first occupation Aggravation does not last indefinitely

Lane,<sup>4</sup> in his discussion of the papers by White, Weidman and Williams read before the American Dermatological Association at the Golden Anniversary Meeting in Philadelphia, made the following remarks

I believe that in the cases of epidermophytosis due to injury two classes will be found In the first group are cases in which the industrial factor is the prime consideration In the last year I saw a man who was a wool puller in one of the shops in Boston, who had, I believe, a fungous infection due directly to his work

There is another group in which the infection occurs as a complication of a preexisting injury or dermatitis of industrial origin, but these infections will be classed as due to injury, and for them compensation can be claimed I have seen a case of this type in a treeer in a shoe shop who had a definite dermatitis associated with his work The condition cleared up almost completely and then intradermal vesicles developed on the lateral surfaces of the fingers with fairly sharply outlined patches on the hands I was not able to obtain the fungus in the case, as I was in the first, but still I reported it as a definite complication of industrial disease I believe this is by far the largest of the two groups that I have mentioned for I have seen several such cases

In our opinion this recurrent pearly dermatitis is a causally related complication of a previous chronic irritation of the skin originating in industrial or private life Current dermatologic opinion unanimously agrees that pompholyx is a constitutional disorder which has no relation to a previous dermatitis irrespective of cause

Testimony at this time that pompholyx is compensable as a complication of industrial irritation of the skin would subject the dermatologist to the charge that his opinion is contrary to prevailing dermatologic thought Under these conditions, it is our opinion that the acceptance of a new clinical entity of this recurrent pearly dermatitis by the name of "dermatitis margaritata recurrens" is justified

#### ABSTRACT OF DISCUSSION

DR JOHN G DOWNING, Boston I wish to congratulate Drs Blaisdell and Swartz on their excellent presentation All those in industrial dermatologic practice have noted this type of recurrent eruption, and one is at a loss to explain to the insurer why an eruption which one stated would be well in six weeks persists for many months However, I am opposed to introducing this type of recurrence of an old dermatitis as a new entity, for it will involve many complications at hearings at the Industrial Accident Board When a dermatitis persists for over three months, my first thought is "Did I make a correct diagnosis?" My second thought is "Is this a case of pompholyx—cheiropompholyx—dysidrosis, or one of the other well known

<sup>1</sup> Knowles, F C Corson, E F, and Decker, H B Diseases of the Skin, Philadelphia, Lea & Febiger, 1942, p 189

<sup>2</sup> Ormsby, O S, and Montgomery, H Diseases of the Skin, Philadelphia, Lea & Febiger, 1943, p 368

<sup>3</sup> White, R P Occupational Affections of the Skin New York, Paul B Hoeber, 1928, p 78

<sup>4</sup> Lane, C G, in discussion on papers of White, Weidman and Williams, Arch Dermat & Syph 15 467 (April) 1927



vesicular eruptions of the hands so well described by Fred Wise?" In my experience these lesions have also appeared on the inner flexor aspect of the forearms

DR SAMUEL W. BECKER, Chicago This excellent paper is certainly timely. Dr Fred Wise gave a paper on this subject in Philadelphia, and I discussed the problem at the American Academy of Dermatology and Syphilology in 1940 and at the Michigan State Medical Society in 1941.

Some years ago I went through the literature, trying to convince myself as to just what this condition might be. In 1873 Tilbury Fox wrote a paper which is similar to the one by Drs Blaisdell and Swartz.

The patients are of a nervous type and present hyperhidrosis. Tilbury Fox reasoned, we now know wrongly, that the vesicles resulted from a damming up of the sweat ducts. It is now believed that the hyperhidrosis and the eruption are both on a nervous basis. He called the disease "dyshidrosis." In the official nomenclature, it is now called pompholyx.

As I have studied these patients, I believe that this eruption on the fingers, the vesicular eruptions of the palms and the vesiculopustular eruptions which have been called recalcitrant eruptions of the palms and soles all fall in the functional group. In other words, at least at the beginning there is no influence from the outside which has produced the eruptions. The cause is purely internal.

As I have studied the patients, rather than the eruption, I find that they are the type of persons who are entitled to develop functional disease. These patients never show positive reactions to patch tests, which further discounts the idea of external irritation as causative.

However, to make the matter more difficult, these patients do sometimes have positive reactions to tests to metals. I had 2 patients within the last few weeks, 1 of whom was reported to have reacted positively to nickel and 1 to zinc chromate material used on airplane wings. I repeated these tests, and obtained a reaction but not primarily vesicular as seen in epidermal hypersensitiveness. It was primarily erythema plus tremendous edema, and following edema there was secondary vesiculation. So, I do not consider this a positive reaction to a patch test. These patients will also show positive dermal reactions either by the intradermal or by the scratch technic.

I am much more optimistic about treatment than Drs Blaisdell and Swartz. I place these patients on a combination of dermatologic management and treatment for functional disease. I use potassium permanganate wet dressings, calamine liniment and 3 per cent ichthammol ointment. After about a week, crude coal ointment is added. I think 5 per cent crude coal ointment aids more than anything else in making the keratinization of the skin disappear. The patients are advised to take a daily nap. I advise them to buy a sunshine lamp. As a result, many of these patients have been relieved, not always completely. They have occasional recurrences, because, if one assumes that a functional disease represents a perversion of the sense of fatigue, when the ordinary individual would get tired these people have outbreaks of blisters. If, however, they cooperate reasonably well, they get acceptable results.

DR SAMUEL M. PECK, Bethesda, Md. Eruptions on the hands due to fungi are infrequently met with in industry and they can be said to play a relatively unimportant role as the cause of lost time in industry. Unfortunately the diagnosis of dermatophytoses and dermatophytids of the hands is made too frequently

without adequate clinical and laboratory findings to justify this diagnosis.

It has been possible to show that the fact that a fungous infection is present which leads to an allergy to the fungi and their products is no reason for assuming that the affected person is predisposed to other allergic diseases. Fungous infections of the hands and feet play a role as a predisposing factor only by allowing more intimate contact between the living cells and the primary irritant and sensitizers. The same sort of a role is played by cuts and abrasions in the skin. The dermatologist who has not had the opportunity of studying large numbers of workers has a wrong impression of the relative importance of dermatophytosis as a causative factor in loss of time and industry. He is led to such an impression because chronic or recurrent cases with eruptions on the hands and feet accumulate in his office so that in his own clinical material he may see a high incidence of such eruptions differentiated from fungous infections or due to fungi.

Before the authors can be sure that they have a new clinical entity in the syndrome which they are describing, they must prove that the eruption in their cases is neither an epidermatophytid nor an ordinary contact dermatitis. This in my opinion they have failed to do, because neither a trichophyton test nor patch tests have been made in most instances.

DR JOSEPH GRINDON SR., St. Louis. We all are familiar with these cases in which a mycosis can be excluded, and are apt to think that they are due to contact conditions, and probably many of them are due to nickel or whatever it may be, or something in the industries, but in some cases they are not of that sort. I do not care whether they are called pompholyx or given some other name.

I think it was the late Dr Robinson of New York who, a good many years ago, showed that these vesicles were not due to dyshidrosis, not connected with the sweat glands.

There is one type of this disease which is rare, but I think you have all occasionally encountered it, that is an eruption affecting one finger of one hand, which has recurred for many years. About forty years ago Blaschko of Vienna, I think, called it herpes digitalis, which is a good name for it. In those cases and in other cases of vesicular eruption of the palms and fingers in which one can assign no probable cause I use a method which has been successful in a number of cases. I use neither local application nor the roentgen rays nor the ultraviolet ray, but (please don't laugh at me) I give the patients  $\frac{1}{60}$  grain (0.001 Gm) of strychnine three times a day. Sometimes there is rapid recovery. If there have been recurrences, they have not come to my knowledge.

DR SAMUEL AYRES JR., Los Angeles. One brief word to corroborate Dr Blaisdell's findings in these cases in which the eruption continues to recur after the patient apparently is well. It undoubtedly is a non-specific sensitivity that has persisted, or I think it is following the original contact irritation.

I do not think that Dr Becker's statement that a reaction to a test with a piece of nickel or zinc chromate is merely because it shows redness or edema and no vesicles is not considered positive should go without question. I think it is too important a matter in the question of industrial dermatologic practice. The insurance companies would like to have the dermatologist say that the reaction to a patch test was negative if vesicles did not appear. I think, for the record, that point ought to be made.

DR. JACOB SWARTZ, Boston. Both Dr Blaisdell and myself wish to thank those who have discussed this

paper. We expected a good many more hot blows, I guess we got off lightly. We realize the risk we took in describing an entity, but this particular disease we do see in Boston, and I was happy to hear that you see it in other places. It is a typical clinical condition, as I will mention in a few minutes. In our cases, we did not see the eruption on the inner aspect of the elbows or forearm as Dr. Downing mentioned.

The functional aspect Dr. Becker stated. I am particularly interested in functional dermatosis. Although I have not written on the subject, I have studied such cases carefully. In these particular patients we have not noted, at least emotionally and otherwise, the findings that we noted in the cases of atopic dermatitis or neurotic excoriations. Cheiropompholyx resembled our described entity the closest. But, as already stated in our paper, such authorities as Ormsby, Knowles, Prosser, White and others specifically state cheiropompholyx is not causally related to industry or chronic irritation but is the result of a constitutional disease to which it is related.

Wise and Wolf in the *New York State Journal of Medicine* in November 1940, discussing the diagnosis and treatment of recurrent vesicular eruptions of the hands, state "In cheiropompholyx there is no history of contacts." In this entity there is a history of a preceding industrial dermatitis or, as in the case of the housewife, a continuous exposure to irritants or sensitizing agents.

Against the argument that this entity is a simple contact dermatitis are the following facts:

1 Absence of lesions on the dorsum of the hands and other areas particularly involved in the case of contact dermatitis.

2 Absence of preeruptive erythema.

3 Presence of deep-seated, pearly vesicles.

4 Absence of eczematization subsequent to regression of lesions.

5 Periodicity of relapses and remissions after the avoidance of the original contacts which brought on the attack of acute dermatitis that preceded this clinical picture. The periodicity is characteristic in these cases.

This entity is not an 'id,' because there is no clinical evidence of an active fungous infection on the feet and elsewhere on the skin, and we looked for it closely, unless one argues a discolored fifth toe nail, which most likely harbors the organism, is the focus for the id. Such a possibility is most unlikely.

Against the theory that these pearly vesicles are the result of bacterial invasion on previously injured skin are:

1 Absence of clinical inflammation such as erythema, pustulation and crusting.

2 In the few cases tried, negative results obtained in an attempt to reproduce such lesions by inoculating into the skin in adjacent areas the contents of the pearly vesicles.

We realize it is rather confusing to start a new name and new entity, but is it not more confusing to have Dr. X talk about this disease under a certain name or type and Dr. Y under other names, as we have seen here, and not understand each other? Is it not better to call it one name so we can understand each other? Then, perhaps, the causation will be found faster.

# NEVUS SEBORRHEICUS ET SUDORIFERUS

## A UNILATERAL LINEAR PHYSIOLOGIC ANOMALY

HARRY L. ARNOLD JR, MD

HONOLULU, TERRITORY OF HAWAII

Simple hyperplasia-hypertrophy and hypersecretion of the sebaceous and sweat glands in a circumscribed area of skin do not appear to have been mentioned in any published account of nevi and adenomas of the sebaceous or sweat glands

Woolhandler and Becker<sup>1</sup> have clearly divided the sebaceous gland overgrowths into the following categories

- Adenoma sebaceum (Balzer)
- Adenoma sebaceum (Pringle)
- Acquired (senile) adenoma sebaceum
- Keratotic adenoma sebaceum
- Sebaceous gland adenoma
- Nevus sebaceus
- Nevus pigmentosus et sebaceus

Whatever this nomenclature may leave to be desired, the categories themselves are reasonably clearcut, and the case to be reported here does not correspond to any of them. These authors did suggest that hyperplasia of sweat glands may on rare occasions be associated with nevus sebaceus, but in that lesion the sebaceous glands are so large and numerous as to form yellowish papules or masses, and the basal layer of the sebaceous acini is found to be absent in sections studied histologically. Becker and Obermayer<sup>2</sup> naturally (and more recently) concurred in this view and amplified it somewhat.

Wolters<sup>3</sup> confirmed the statement about the occasional association of hyperplasia of sweat glands with nevus sebaceus, his patient, however, did not appear to have shown evidence of active hypersecretion of either sweat or sebum.

Way<sup>4</sup> and Warren and Warvi<sup>5</sup> did not refer to any lesion of the sebaceous glands character-

ized by hyperplasia and hypersecretion, much less by concomitant hypersecretion of sweat.

Linear unilateral nevi consisting principally of sebaceous glands or of comedos have been reported many times. Sweitzer and Winer<sup>6</sup> have summarized the literature (some 30 cases) on nevus unilaterialis comedonicus, which typically has a linear and unilateral pattern but consists solely of dry comedos with or without surrounding inflammation and hypoplastic or even absent sebaceous glands. Cohen<sup>7</sup> has re-



Fig 1—Linear configuration of the lesion, hypopigmentation, comedos and the huge droplets of sweat limited to the involved area

ported such a case under the name nevus acneiformis unilaterialis. The sweat glands are apparently unaffected in this disease. Poor<sup>8</sup> was cited by Stelwagon<sup>9</sup> as having concluded that there

1 Woolhandler, H. W., and Becker, S. W. Adenoma of Sebaceous Glands (Adenoma Sebaceum), *Arch Dermat & Syph* **45** 734 (April) 1942

2 Becker, S. W., and Obermayer, M. *Modern Dermatology and Syphilology*, Philadelphia, J. B. Lippincott Company, 1940, p. 579

3 Wolters, G. Ueber ein Fall von Naevus epithelomatous sebaceus capitis, *Arch f Dermat u Syph* **101** 197, 1910

4 Way, S. The Sebaceous Glands. Their Histopathology and Role in Diseases of the Skin, *Arch Dermat & Syph* **24** 353 (Sept) 1931

5 Warren, S., and Warvi, W. N. Tumors of Sebaceous Glands, *Am J Path* **19** 440 (May) 1943

6 Sweitzer, S. E., and Winer, L. H. Nevus Unilaterialis Comedonicus. Nevus Follicularis Keratosus of White, *Arch Dermat & Syph* **26** 694 (Oct) 1932

7 Cohen, E. L. Nevus Acneiformis Unilaterialis, *Brit J Dermat* **55** 297 (Dec) 1943

8 Poor, cited by Stelwagon<sup>9</sup>

9 Stelwagon, H. W. *A Treatise on Diseases of the Skin*, Philadelphia, W. B. Saunders Company, 1910, p. 639

is a type of nevus sebaceus, which he called nevus sebaceus circumscriptus asymmetricus, which is usually linear. It does not appear, however, that this lesion is associated with abnormality of the sweat glands. It was probably an example

of the same type that was reported by Maloney<sup>10</sup> as nevus sebaceus linearis, which he described as consisting of yellowish closely set papules, some topped by comedos, histologically indistinguishable from adenoma sebaceum.

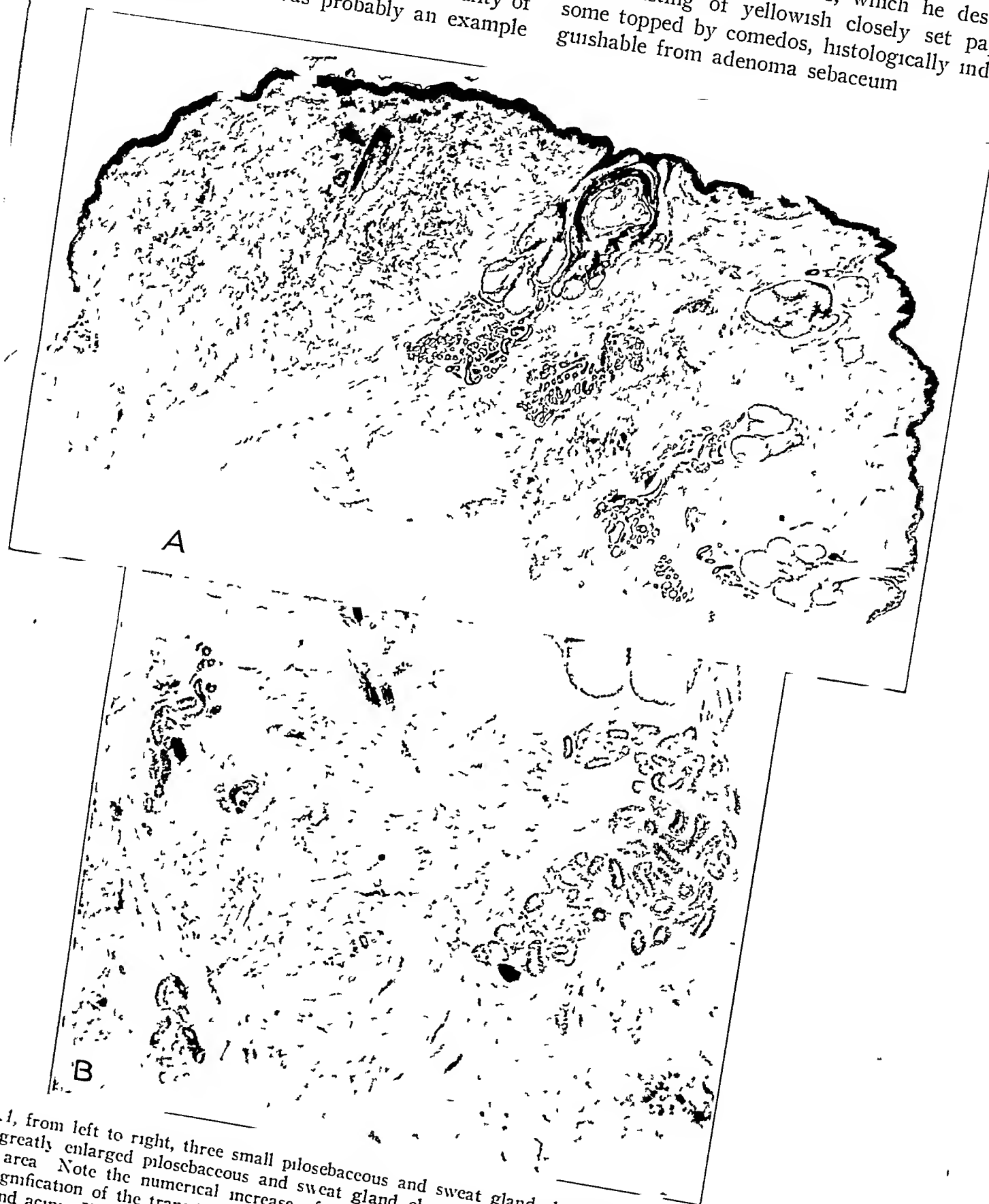


Fig 2—1, from left to right, three small pilosebaceous and sweat gland elements outside the lesion and four consecutive, greatly enlarged pilosebaceous and sweat gland elements, one showing an obliquely cut comedo, in the involved area. Note the numerical increase of the coils of the sweat gland. Hematoxylin and eosin,  $\times 6$ .  
B, higher magnification of the transition from normal to abnormal glands. Note the striking difference in size of the sweat gland acini. Hematoxylin and eosin,  $\times 20$ .

<sup>10</sup> Maloney, E. R. Nevus Sebaceus Linearis (Case Presentation), Arch Dermat & Syph 30 167 (July) 1934

As to the reported association of abnormality of the sebaceous glands with hypersecretion or hypertrophy of the sweat glands no such lesion

was mentioned by Gates, by Warren and Warvi<sup>11</sup> or in Suttons'<sup>12</sup> or Becker's<sup>2</sup> texts

#### REPORT OF A CASE

T S, a 20 year old Japanese man, was first seen in December 1943 because of a lesion on the left side of his neck which had been present for nearly three years. It had caused no itching or pain but was periodically annoying to him because of its extreme moistness and oiliness and because of the blackheads that frequently developed in it.

Examination disclosed a healthy, athletic-looking young Japanese man whose skin was clean and free from significant lesions, he had in particular no acne or dandruff. On the left side of his neck, about 5 cm below and posterior to the ear, there was a sharply outlined, irregularly oval hypopigmented macule about 3 by 4 cm, which extended forward and upward along a path about 1 cm broad to a point just anterior to the tragus of the ear. This macule was decidedly moister than the surrounding skin and was studded with numerous large soft greasy comedos. While the lesion was being photographed, it was observed under the heat of the lights to become beaded with huge droplets of sweat, far out of proportion to the amount of perspiration on the surrounding skin (fig 1).

Biopsy was performed, and the sections showed that the pilosebaceous elements within the lesion were many times larger than those outside it and each had immediately underlying it one or two large coil gland acini (fig 2). There were no other significant changes noted. Dr Fred Weidman, to whom sections were sent, expressed the opinion that the coil glands appeared to be in the exhausted rather than in the resting stage.

#### COMMENT

The indolence of this lesion, its sharp localization, its unilateral and linear configuration and

11 Gates, O, Warren, S, and Warvi, W N. Tumors of Sweat Glands, *Am J Path* 19 591 (July) 1943.

12 Sutton, R L, and Sutton, R L, Jr. Diseases of the Skin, ed 10, St Louis, C V Mosby Company, 1939.

its lack of any apparent causative factor all support the view that it is a nevus, notwithstanding its having first appeared when the patient was 17 or 18 years old. There is nothing about the histologic changes to contradict this view, and indeed they completely fail to support any other, certainly they show no evidence of neoplasia. The degree of hypertrophy or hyperplasia of the glands is far from sufficient to warrant classifying the lesion as an adenoma.

As nearly as can be judged, the sebaceous and sweat glands appear to share about equally in the process, neither seems to be enlarged out of proportion to the other.

Finally, the most striking aberration from the normal is in the function of these glands rather than in their structure, the profuse outpouring of sweat under the influence of external heat (or physical exertion) is remarkable, though no more so than the continued outpouring of sebum evidenced by the greasiness of the lesion and by the large soft greasy comedos occupying almost every hair follicle.

#### SUMMARY AND CONCLUSIONS

A linear unilateral lesion in which the sweat and sebaceous glands were larger and much more actively secreting than those in the surrounding skin was observed.

This lesion seems to represent an aberration of function rather than of structure, it appears to be a physiologic secretory nevus involving the sebaceous and eccrine glands of the skin.

Dr I L Tilden, of the Department of Pathology of The Clinic, Honolulu, made the photograph, prepared the histologic sections, and made the photomicrographs. The Clinic, 881 South Hotel Street.

# DEMENTIA PARALYTICA AND WASSERMANN REACTION OF THE SPINAL FLUID

ADOLF KRAKAUER, M D

CLARINDA, IOWA

It is the consensus of physicians treating dementia paralytica that an indispensable factor in support of the diagnosis is a positive Wassermann reaction of the spinal fluid. The literature dealing with the serologic reaction reflects the same idea. Wechsler<sup>1</sup> stated that "the blood and, especially, spinal fluid Wassermann are positive in practically 100% of cases." According to Stokes,<sup>2</sup> "The negative spinal fluid is better presumptive evidence of the absence of syphilis in the neurological field than is the negative blood Wassermann reaction in general medicine." He concluded that "a negative spinal fluid, even in the presence of a neurological condition, almost excludes general paresis from the diagnosis." Stokes continued "The question of the existence of seronegative paresis is as yet undecided, but there are some indications that general paresis in a preponderately vascular phase may be almost, if not quite, seronegative in the spinal fluid, at least after treatment, and still be active and symptomatically progressive. Cases of this sort, however, are so rare that they need hardly enter into the diagnostic rules applicable to ordinary practice." Becker and Obermayer<sup>3</sup> postulated unequivocally that "in typical paresis the test is always strongly positive throughout all concentrations." Grinker<sup>4</sup> confirmed this and elaborated that statement by adding that "if only 0.22 cc of fluid is required to give a positive reaction, there is great probability that the patient is suffering from either paresis or taboparesis, it is much less probable that he is the subject of other neurosyphilis or beginning tabes. In many more cases of neurosyphilis and tabes the Wassermann reaction becomes positive by the use of larger quantities

of fluid from 0.4 to 1 cc." But he pointed out "that in general paresis the cerebrospinal fluid gives a positive reaction with the smallest quantity 0.05 to 0.2 cc a possible point of differentiation from other types of neurosyphilis. An additional point is the fact that not only is the positive Wassermann reaction seen in its greatest intensity in general paresis, but once present it is with difficulty changed into a negative one and often becomes Wassermann fast. In our opinion whenever a case clinically diagnosed as general paresis presents negative findings in blood and cerebrospinal fluid, the diagnosis of paresis should be reconsidered until such time as further examination shall either prove or disprove the clinical diagnosis." These quotations could easily be augmented and substantiated by statements of many other authors in the international literature as well as by the conclusions of any practitioner dealing with dementia paralytica.

These rules seem acceptable only with certain reservations, however. In the following series of cases deviations from the aforementioned observations became evident. The patients were seen exclusively at the Clarinda State Hospital within a few months previous to the writing of this report. In the histories all details which have no bearing on the Wassermann reactions of the spinal fluids are omitted. All serologic procedures were performed at the Iowa State Department of Health, Iowa City, the vast experience of whose staff guarantees accurate results. Care was taken that antisyphilitic treatment which might have influenced our tests was not given at the time.

CASE 1—A B C was treated for eight months in 1939 at the University Hospitals, Department of Neurology, State University of Iowa. At that time encephalograms showed slight cortical atrophy. He had an intelligence quotient of 84 (dull normal). The diagnoses were neurosyphilis and dementia paralytica. The case was rather unusual in the absence of a positive Wassermann reaction of the spinal fluid, but the positive colloidal gold curve, the general history and other evidence all bore out the diagnosis. There was no evidence of gumma or tumor. In December 1939, in Clarinda State Hospital, his neurologic status, including the pupillary reactions, was found to be still normal, but he exhibited epileptiform seizures, showed destructive and suicidal

From the Clarinda State Hospital

1 Wechsler, I S. Textbook of Clinical Neurology, ed 4, Philadelphia, W B Saunders Company, 1939, p 469

2 Stokes, J H. Modern Syphilology, Philadelphia, W B Saunders Company, 1939, p 161

3 Becker, S W and Obermayer, M E. Modern Dermatology and Syphilology, Philadelphia, I B Lippincott Company, 1940 p 750

4 Grinker, J. Syphilis of the Nervous System, in Tice, F. Practice of Medicine, Hagerstown, Md W F Prior Company, Inc, 1935, vol 9, chap 8, p 799



tendencies and became self assertive. The patient had no insight concerning his mental condition, but he showed remnants of intelligence. In the following year the seizures increased, and he became confused and irritable. In 1941 he received malaria therapy and improved considerably. His seizures ceased with adequate treatment and did not reappear when use of the drugs was discontinued. His mental condition grew so favorable that he could be paroled, he was and is able to make a living by holding a job. During 1943 the Wassermann reaction of the blood became positive again after having been negative repeatedly in 1941 and 1942. Chemotherapy was started once more. The neurologic findings remained negative, and he appeared in satisfactory mental condition throughout this time. Results of the tests of the spinal fluid were <sup>5</sup>

	Wassermann Reaction	Colloidal Curve	Cells	Globulin
4/13/39	Negative	5550400000	9	Negative
11/25/39	Negative	0000000000	2	Negative
9/22/42	Negative	00000	8	Negative
3/ 8/43	Negative	11000	2	Negative

The patient is now in excellent physical condition.

CASE 2—G C was admitted to the hospital in June 1942. His pupils were unequal and reacted sluggishly to light and in accommodation, the Romberg test elicited a moderate response, the right patellar reflex was present, but the left one was missing. The patient had auditory hallucinations, he was forgetful, especially in regard to recent events. Besides, he was delusional and confused, and his orientation and intelligence were poor. At times he was violent. His syphilis had been acquired nineteen years before. The antisyphilitic chemotherapy he had received had been insufficient. The serologic tests of the blood at the time of his admission, October 20, showed positive Kolmer, Kahn and Kline reactions. In tests of the spinal fluid, the Wassermann reaction was found to be negative, faint traces of globulin were observed, 8 cells were counted and the colloidal mastic curve was 55430. He was treated with a course of oxophenarsine hydrochloride, tryparsamide, thio-bismol and potassium iodide till February 1943. He calmed down greatly, but speech was slurred and he showed progressing mental deterioration. The serologic reaction of the blood in February 1943 was again positive in the Kolmer, Kahn and Kline tests. The Wassermann reaction of the spinal fluid was now positive, there were 8 cells and faint traces of globulin, and the colloidal mastic curve was 55430. The patient was inoculated with malaria at that time, but he died one month later. The physical and mental observations, the results of laboratory investigations of blood and spinal fluid and the subsequent course of the disease prove the diagnosis of dementia paralytica beyond doubt. It was also proved by the positive Wassermann reaction of the spinal fluid in February 1943, but on his admission the same reaction had been negative.

CASE 3—H B was admitted to the hospital in October 1940. He had had syphilis for four years, and several courses of antisyphilitic chemotherapy in 1940 had produced negative Wassermann reactions of the blood and spinal fluid. In the spring of 1942 the Wassermann reaction of the blood became positive again. Mental changes were observed in the same year, such as forgetfulness, grandiose ideas about money, recklessness in driving and evidence of a fighting spirit. These symptoms turned to worry about financial affairs. He

had a feeling of inferiority and a tendency to isolate himself. Furthermore, he suffered from insomnia. The physical observations at the time of his admission disclosed the following picture. The pupils were normal, the Romberg sign was not elicited, and the patellar reflexes were present. The reactions of the blood in the Kolmer and Kline tests were negative. On Oct 15, 1942 the Wassermann reaction of the spinal fluid was doubtful, five days later, on October 20, however, it was negative, although no therapy of any kind had been given between these dates. Besides, the spinal fluid showed 14 cells, the globulin reaction was positive for dementia paralytica, and the colloidal mastic curve was 55432. The diagnosis was based on the unmistakable mental picture and on the reactions of the spinal fluid. The further course of the disease also favored the diagnosis. After preliminary treatment with tryparsamide, mapharsen and thio-bismol, malaria treatment was begun, and after thirteen chills the same chemotherapy as before was administered. The patient improved so much that in April 1943 he could be discharged in care of the family physician as a normally reacting person.

CASE 4—A B was admitted to the hospital in September 1939 with the diagnosis of dementia paralytica. Mentally he had shown forgetfulness, childish behavior, irritability and the habit of talking to himself. He was always irrational, optimistic and joyous. This condition did not change. The physical signs were unequal but round pupils which reacted not at all to light and only sluggishly in accommodation, slight intentional tremor but no ataxia and good coordination. The following serologic reactions were observed. The reaction of the blood was positive in the Kolmer and negative in the Kline test, the Wassermann reaction in the spinal fluid was negative. Six months later the reaction of the blood was doubtful in the Kolmer test but was negative in the Kahn and Kline tests. The mental picture has not changed up to the time this report was written. The diagnosis was based on the patient's mentality and on the slightly abnormal pupillary reactions, but it is not absolutely beyond doubt and is open to criticism. In December 1942 the spinal fluid showed 8 cells, the globulin reaction was negative for dementia paralytica, and the colloidal mastic curve was 32100. Results of these tests were favorable, although no malaria treatment or chemotherapy had been applied.

CASE 5—A L was admitted to the hospital in January 1943. Her mental disturbances had begun a year previously with abnormal worrying about financial matters, she was noisy and talkative and frequently sang. At the same time the patient became aggressive, often she had crying spells. Later she was quiet and isolated herself. She repeatedly uttered hypochondriac complaints of various kinds. Her speech was slurred at times. The only abnormal physical signs were a rather poor coordination and high knee reflexes. In February 1943 there were positive reactions of the blood in the Kolmer, Kahn and Kline tests. In the spinal fluid, the Kolmer reaction was negative, there were 10 cells and no excess globulin, the colloid mastic curve was 43210. With antisyphilitic chemotherapy, which preceded and followed the treatment with malaria, the patient improved. She is still under an antisyphilitic regimen. The serologic reaction of the blood remains positive. Close daily observation of her mental condition corroborates the diagnosis of dementia paralytica, although it is somewhat questionable when all physical and serologic evidence is considered.

CASE 6—B B was a "doorstep" child, having been found in 1919, with signs of prenatal syphilis, gonorrhea and otitis media. Her upper incisors were

<sup>5</sup> These tests were made at the Clarinda State Hospital, where since 1942 the colloidal mastic curve has been used instead of the colloidal gold curve.

notched The Wassermann reaction of the blood was positive in 1921 when tested on at least seven different occasions, it became negative after intense antisyphilitic chemotherapy with neoarsphenamine and with preparations of mercury and of iodine. It became positive again and remained so in spite of thorough treatment and malarial therapy in September and October 1942. Therefore more chemotherapy was given. In July 1937 the spinal fluid had been examined at the Iowa City University Hospitals and was found normal in every respect. In June 1942 the right pupil was slightly irregular, but there was normal reaction on both sides, the fingers showed poor coordination. The spinal fluid again was normal in June 1942, the reactions of the blood in Kolmer, Kahn and Kline tests were all positive. The mental picture showed severe changes. The patient, who had been reared in a law-abiding, well-to-do family and had enjoyed the best education, stole a car, sold it, borrowed \$530 under false pretense and became egocentric, quarrelsome and absolutely amoral. She had grandiose ideas, was forgetful and irritable and had outbursts of temper. She called herself oversexed and also showed homosexual tendencies. During treatment she improved considerably and could be paroled in 1943 in care of her foster parents and the family physician.

CASE 7—C O was admitted to the hospital in January 1943 with the diagnosis of dementia paralytica. There were signs of involvement of the pyramidal tract, there was a fine tremor and poor coordination of the extremities. The Romberg sign and the Babinski reflex were elicited, as was the foot clonus. The patient was forgetful, he had loss of memory and of initiative. His intellect and judgment were impaired, and he was disoriented as to time and place. The reactions of the blood in the Kolmer, Kahn and Kline tests were positive and remained so even after intense antisyphilitic chemotherapy was applied and after he had been inoculated with malaria. But before any treatment had been started, the spinal fluid showed a negative Wassermann reaction, 6 cells and a colloid mastic curve of 55554. The patient, who is still under treatment, has improved considerably but is not yet normal.

#### COMMENT

The cases mentioned were observed during a relatively short period. It is possible that one could find an even larger series at this hospital alone, were it not for the fact that not all registered patients can be reexamined frequently, for reasons common to all institutions in these days. As stated before, a strict critic might find reason for debate concerning some of these cases. Much will depend on how far the mental picture can be considered as a deciding factor in the diagnosis of dementia paralytica. In a syphilitic patient an anorganic psychosis can always develop, either before or after his infection. But if one observes the signs and symptoms of dementia paralytica, it is rather difficult to refute a relationship of the syphilis with the psychotic fea-

tures. Dementia paralytica may well be the cause in any given case, even though some of the fundamental signs of this disease are missing.

A thorough study of the literature previously cited reveals that some authors qualified their statements concerning the necessity of a positive Wassermann reaction of the spinal fluid by describing it as being only "almost" or "nearly" indispensable. In the first case reported here, the Iowa City University Hospitals established the diagnosis of dementia paralytica, emphasizing that the Wassermann reaction of the spinal fluid was negative.

I certainly do not wish to convey the impression that this report of a few cases, some of which may be questionable, is intended to overthrow a doctrine which has been fortified by hundreds and thousands of examples and which has led a man like C O Cheney<sup>6</sup> to describe patients with dementia paralytica as persons "showing rapidly or slowly progressive organic intellectual and emotional defects with physical signs and symptoms of parenchymatous syphilis of the nervous system and completely positive serology including the positive gold curve." In order to modify such well based conclusions, much larger series of cases would have to be examined and numerous statistics would have to be compiled. But the deviations from the usual are worth recording and present a stimulus for further investigation. I believe that the majority of persons with dementia paralytica in the United States are admitted to state institutions. If the patients treated in some of these hospitals should be checked from this serologic point of view, the purpose of this paper would be accomplished.

#### SUMMARY

It is suggested in the literature that dementia paralytica rarely occurs in association with a negative Wassermann reaction of the spinal fluid.

Seven cases were observed at the Clarinda State Hospital, Clarinda, Iowa, which may bear out the suspected possibility that dementia paralytica may coincide with a negative Wassermann reaction of the spinal fluid.

It is considered possible that a number of similar cases could be found and that it is of importance to study the problem further.

<sup>6</sup> Cheney, C O. *Annals of the National Committee for Mental Hygiene* ed 10, New York, National Committee for Mental Hygiene, 1942.

# MELANIN PRODUCTION IN SKIN

## II FURTHER HISTOCHEMICAL OBSERVATIONS

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An earlier report<sup>1</sup> dealt with the influence of protoplasmic poisons, such as potassium cyanide and sodium fluoride and of alkalinity on the Meirowsky phenomenon (the increase in epidermal pigment in excised or cadaver skin when incubated at 37 C and higher or on exposure to ultraviolet rays). These poisons served to accelerate the formation of pigment. It was further reported that in the experiment in which the solution containing the skin sections was overlaid with liquid petrolatum there was demonstrated an increased acceleration in pigment production. On the basis of this evidence it was suspected that atmospheric oxygen possibly was not required for the production of this phenomenon.

Earlier investigators of this phenomenon all came to the conclusion that atmospheric oxygen was required for its elicitation. The most recent and comprehensive studies of this problem, by Miescher and Minder<sup>2</sup> and, incidentally published before the presentation of our<sup>1</sup> first paper, confirmed the earlier conclusions. Despite the unanimity with which we are confronted, we are led by our studies to question the truth of the conclusions of the earlier investigators<sup>3</sup> and to affirm that the phenomenon of Meirowsky can be produced without the aid of atmospheric oxygen. Since most speculative thinking about human pigment and the method of its produc-

tion centers about the available pertinent facts evolved experimentally, it is important that all these facts be probed thoroughly and, particularly, that a detailed record be made of the investigative procedures followed.

The several reported<sup>1</sup> significant procedures followed by us in producing the Meirowsky phenomenon are briefly summarized in the following paragraph.

Sections of frozen skin, hardened for less than twenty-four hours in solution of formaldehyde U S P diluted 1 to 10, were placed in open beakers and incubated for three hours at 37 and 56 C. The sections were immersed in the following solutions, with and without an overlaying of the aqueous solution with liquid petrolatum: (1) 0.85 per cent sodium chloride, (2) 0.1 per cent potassium cyanide and (3) 0.1 per cent sodium fluoride. Further, all three solutions were variously buffered with phosphate to give  $p_H$  values of approximately 5, 6, 7, 8 and 9.

It should be noted that our original contribution to the studies of this phenomenon was the demonstration of the efficacy of protoplasmic poisons to enhance the degree of pigment production, and that the only similarity of our procedures to those of earlier investigators was the part of our reported practice in which we incubated the frozen sections in isotonic solution of sodium chloride.

In probing the report of the suppression of a reaction, the investigator must distinguish among the fact of suppression, the procedures used and the explanations offered for its accomplishment. And so, without denying any of the earlier reports of suppression of the Meirowsky phenomenon, we challenge the correctness of the explanation for the mechanism of its achievement. Incidentally, we can have no insight into the true explanation of the suppression, for we failed to prevent its production.

This research was made possible by a grant from the Dr. Simon Baruch Foundation.

From the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital, Columbia University.

1 Sharlit, H., and others. Histochemical Observations on Melanin Production in the Skin, *Arch. Dermat. & Syph.* **45** 103 (Jan.) 1942.

2 Miescher, G., and Minder, H. Untersuchungen über die durch langwelliges Ultraviolett hervorgerufene Pigmentdunkelung. *Strahlentherapie* **66** 6, 1939.

3 See Miescher and Minder<sup>2</sup> for bibliography.

On us developed the burden not alone of seeking to suppress the Meiwsky phenomenon by a procedure calculated to supply an oxygen-free atmosphere but of establishing acceptable proof that such an atmosphere, free of oxygen, had been present and operating throughout the experiment, in spite of our failure to suppress the phenomenon. We used a nitrogen atmos-

melanin as proof of the effective presence of an oxygen-free atmosphere. Experiments confirmed Minder's experience<sup>4</sup> disclosing that exceedingly small traces of oxygen were difficult to exclude, since it took repeated variations of procedure to acquire a setup that completely prevented the spontaneous conversion of dopa to melanin. Incidentally, such stringent require-

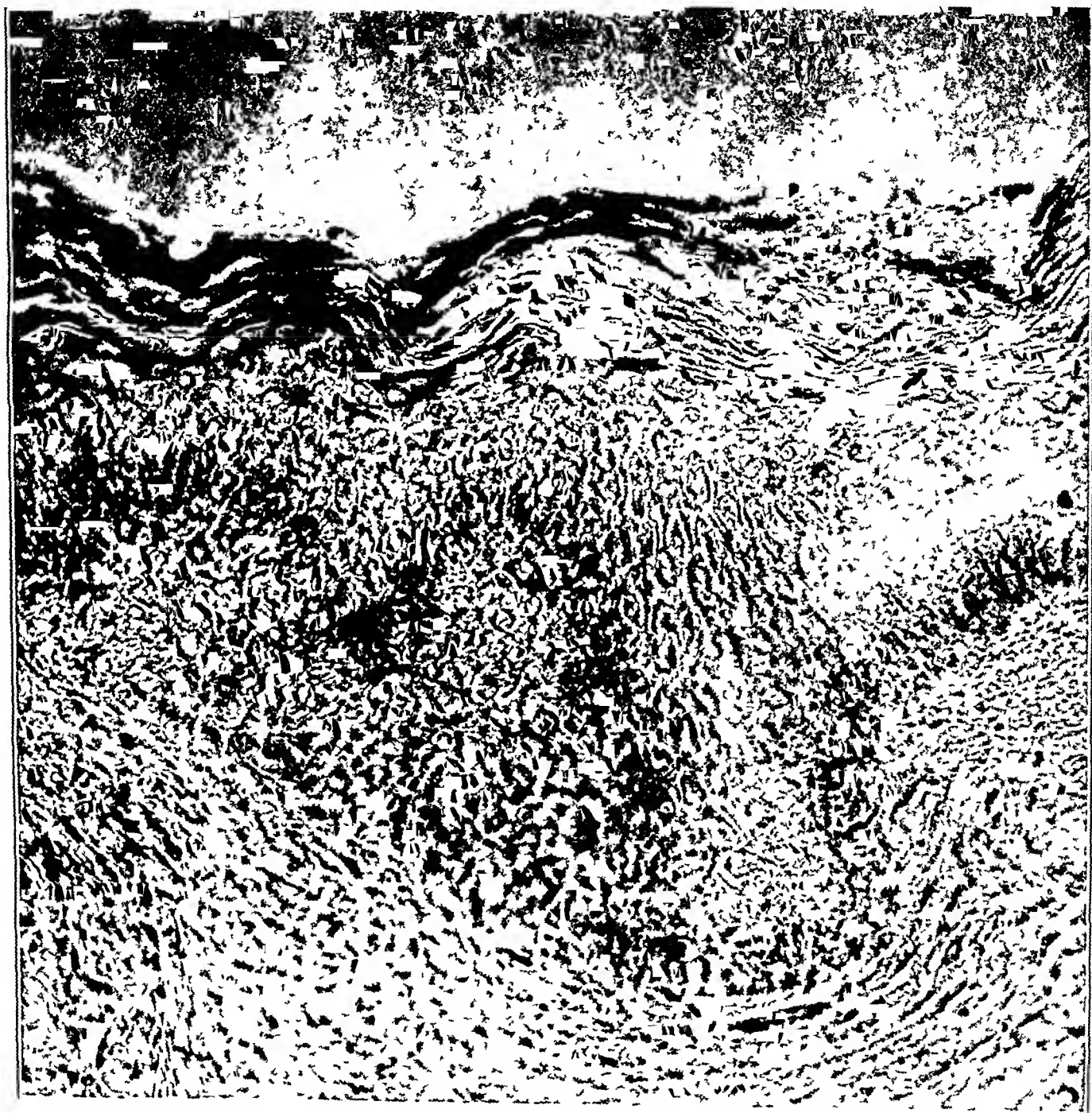


Fig 1—Control section, mounted immediately after cutting from the frozen block, discloses the amount and location of pigment originally present in the section

where in which to carry out the incubation of the frozen sections and therefore accepted (1) the inhibition of the enzymatic conversion of para cresol to a melanin by potato tyrosinase and (2) the suppression of the auto-oxidation of a properly buffered solution of dopa to a

ments were not needed to inhibit the production of paracresol melanin

<sup>4</sup> Minder, H. Histochemische Untersuchungen über das Phänomen der Pigmentdunkelung, Inaug. Dissert., Zurich, Gebr. Leemann & Co., 1939



The former procedure, therefore, was the one that we adopted. It consisted of the following steps:

The sections of frozen skin were incubated in flasks containing air-tight rubber stoppers with perforation through which gases could be introduced and withdrawn from within the flasks. After the sections had been

37 C for three hours regularly failed to show any change in color from its original water-clear appearance.

This procedure with dopa was carried out as a control in all experiments. This was the criterion that we had accepted as proof of the presence of an oxygen-free atmosphere.

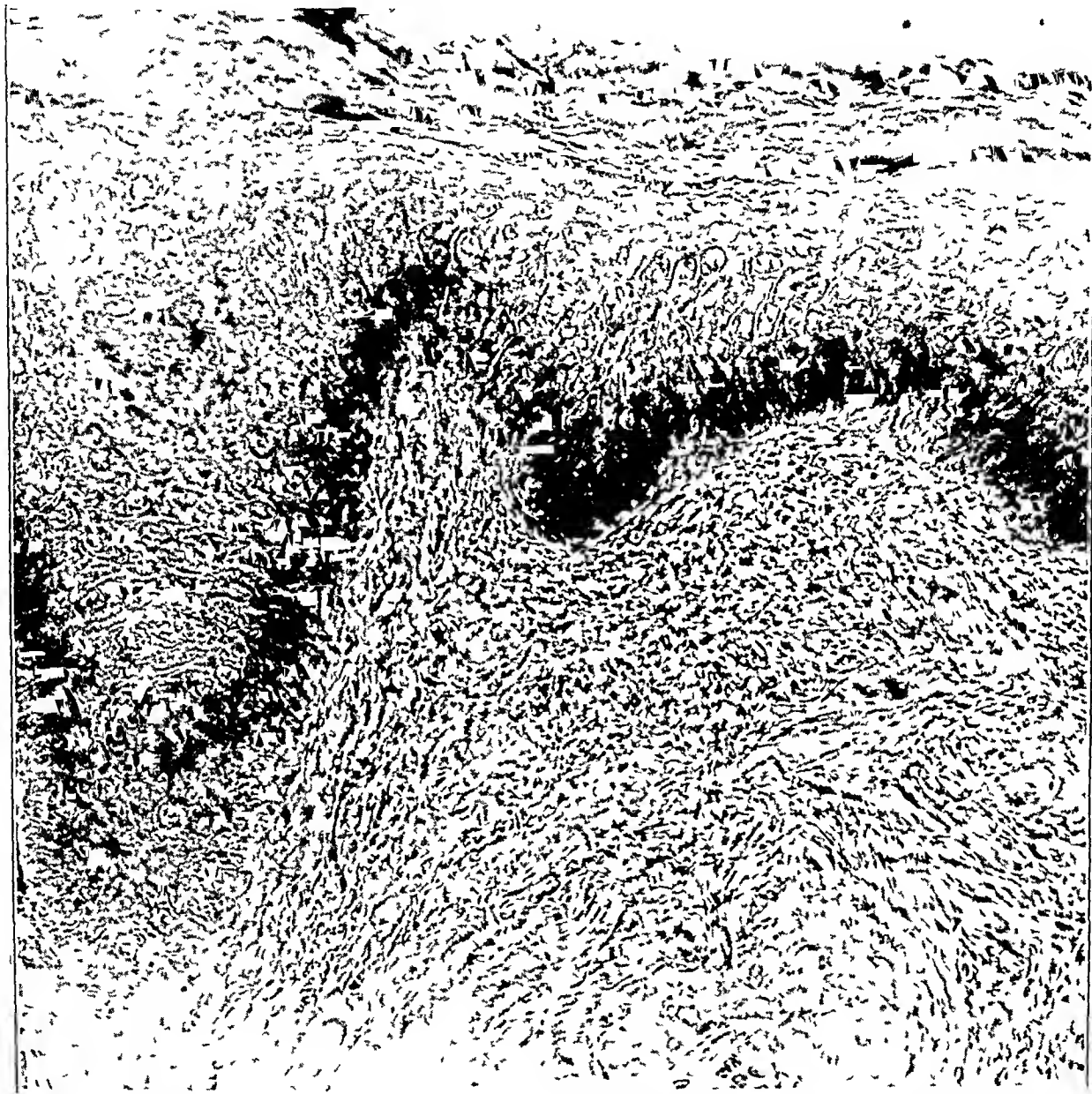


Fig 2—The pigment picture in the epidermis after incubation of the section in isotonic solution of sodium chloride in an atmosphere of air.

placed in the fluids within the flasks, the air was withdrawn from the flasks as completely as possible. Then nitrogen, after being filtered from a tank through a pyrogallol-alkali mixture to remove any trace of oxygen contamination, was driven through the flasks and their fluid contents for about half an hour. The outlets were then sealed and the flasks placed in an incubator for three hours. Dopa solution buffered to  $pH$  7.3, placed in a flask treated in the prescribed manner and kept at

All the experiments included in our first report were repeated according to this procedure. The results, both quantitatively and qualitatively, paralleled those previously reported.

We offered no photomicrographs in our first report. Here we present seven, all of the same piece of tissue, in substantiation of the statement in the preceding paragraph.

The first three photomicrographs apply only to the types of experiment followed by all previous investigators of the Meirrowsky phenomenon. The remaining four reveal the effects of protoplasmic poisons on pigmentation and constitute our original contribution to the experimental data dealing with the phenomenon

that the pigment could be reestablished by a repetition of the incubation in air. They could effect this cycle for a variable number of times, but finally the pigmented phase would become fixed and irreversible. From all these observations relative to the part atmospheric oxygen plays in the production of the Meirrowsky

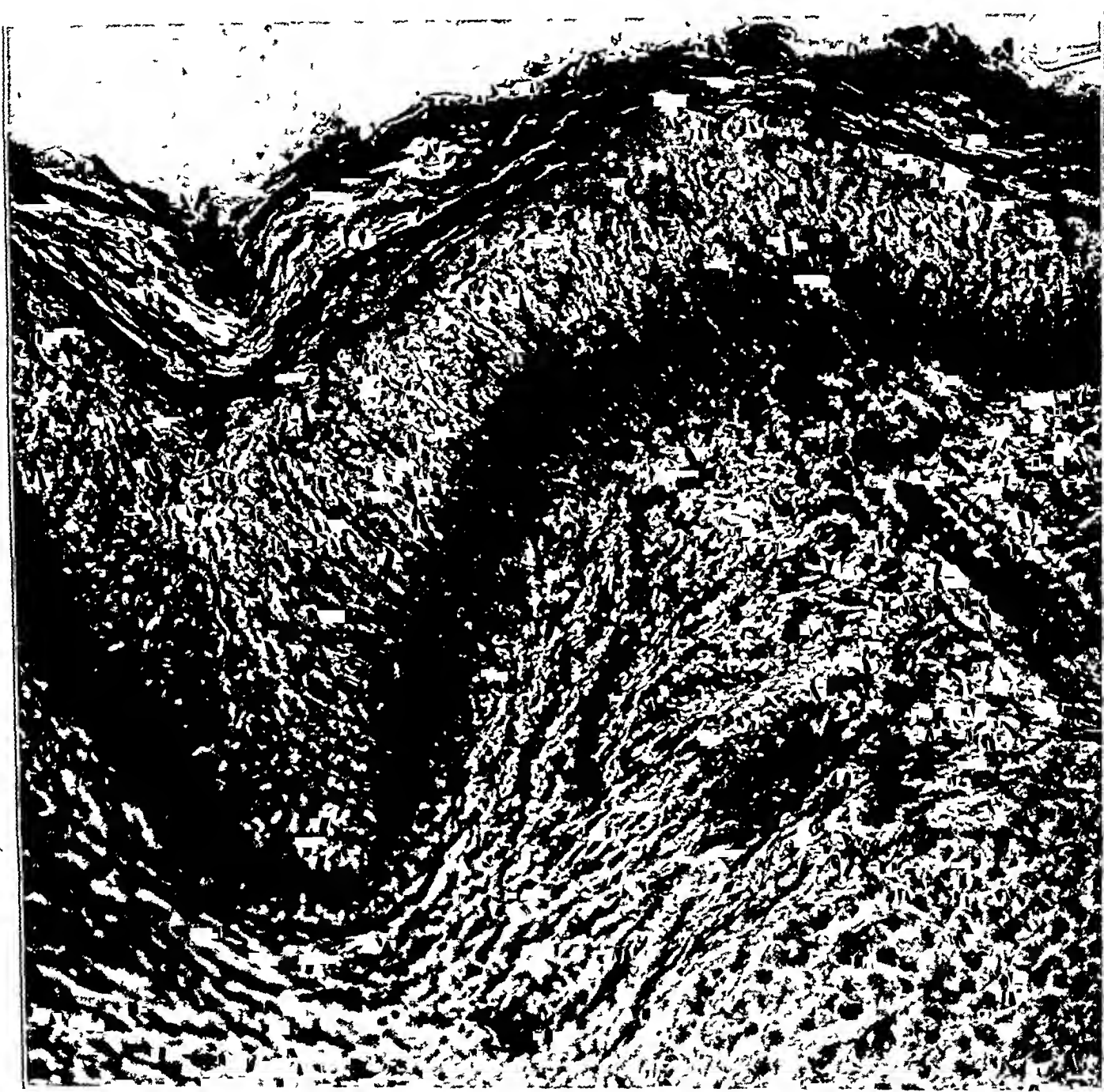


Fig 3—The pigment picture in the epidermis after incubation of the section in isotonic solution of sodium chloride in an atmosphere of nitrogen

The conclusion is inescapable. The original Meirrowsky phenomenon and our reported variations in eliciting it do not depend on an external source of oxygen for their production.

Miescher and Minder further reported<sup>2</sup> that sections of skin in which increased pigmentation has occurred as a result of incubation in air could be decolorized by reducing agents, and

phenomenon, they came to the following conclusions: (1) that this phenomenon of an increased number and size of melanin particles occurring in the epidermis from the basal layer up to the horny layer is simply a result of oxygenation of particles already formed, (2) that melanin exists with all degrees of oxygen saturation, (3) that the size and depth of the



color particle are determined by its state of oxygen saturation (the less the oxygenation, the smaller the particle and the paler the color), (4) that complete oxygen saturation is the stable form, (5) that the phenomenon therefore represents only the exerting of an influence on the size and color of the melanin particles already present, through further saturation of the particles with oxygen, and last (6) that since new

presence of atmospheric oxygen in order to produce the phenomenon? I pose this question in this form because in all likelihood oxidation by means of acceptance of oxygen underlies the production of the phenomenon of Meirrowsky. The conclusions of Miescher and Minder must be modified, in my opinion, to satisfy and offer an explanation for my experimental results, to wit (1) the production of the phenomenon

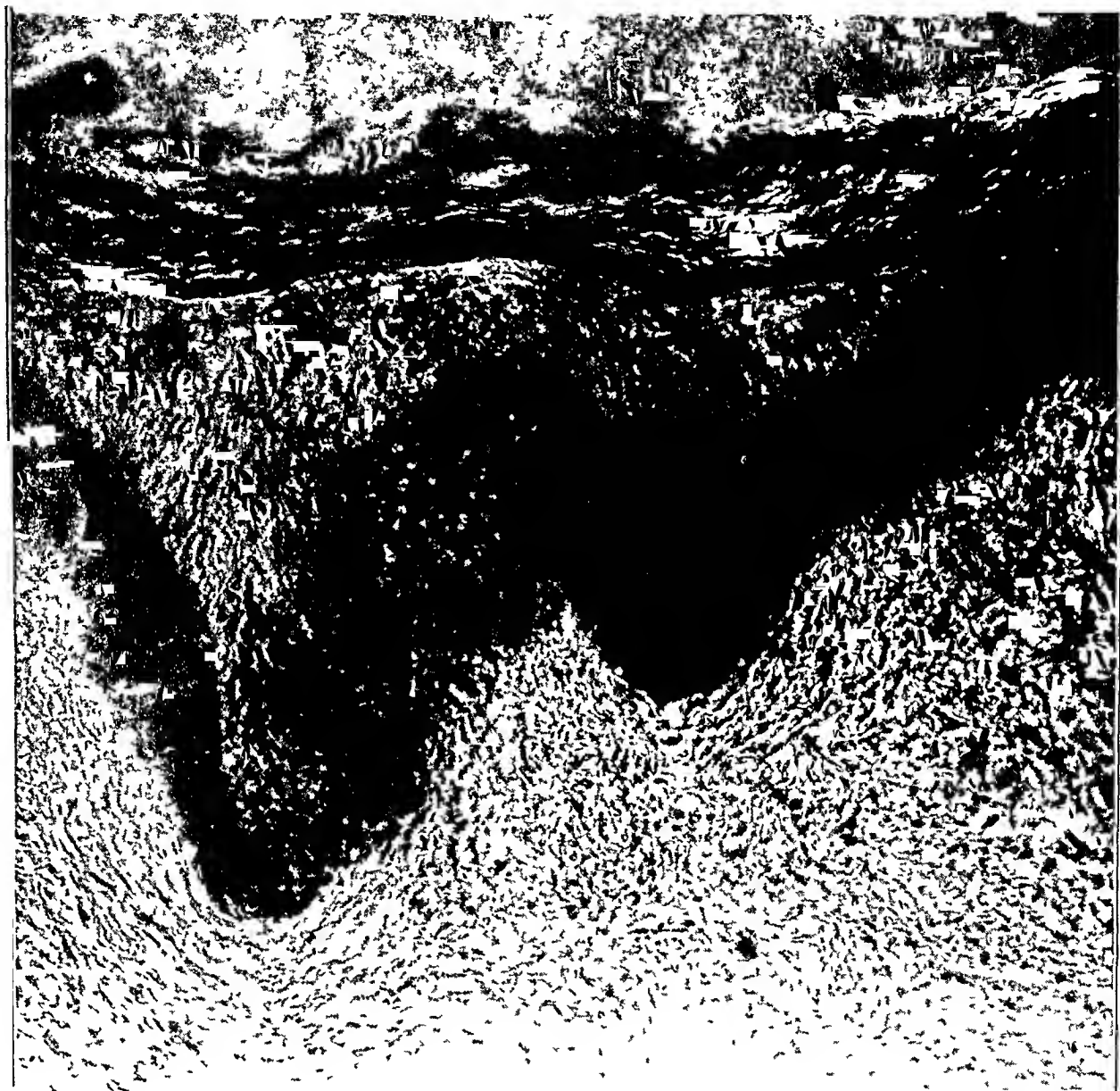


Fig 4—The pigment picture in the epidermis after incubation of the section in 0.1 per cent potassium cyanide solution buffered to  $pH$  9 in an atmosphere of air

ment production is not involved the phenomenon has no bearing on the dopa theory of Bloch, and they therefore preferred to call it a darkening phenomenon

What becomes of these conclusions if one rejects their experimental basis, namely, the

without the aid of atmospheric oxygen and (2) the accentuation of the pigmentary increase by the use of protoplasmic poisons

I offer an explanation in the following terms. The Meirrowsky phenomenon results from (1) the production of more melanin *de novo* in cells

of the epidermis having the capacity normally to form melanin (basal layer) and (2) the enlargement of all the existing particles by means of oxygen saturation through the making available within the cells of ionic oxygen throughout the epidermis. The availability of this oxygen is experimentally achieved by reducing or de-

stroying the functional capacity of the cytochrome system of the cell (primary respiratory chain), which system has a primary call on all available oxygen. The damage to the cytochrome system is produced naturally (1) through death (cadaver skin) (2) by moribundity (excised skin) and experimentally (3) through other denaturing processes (skin submitted to freezing, hardening with solution of formaldehyde, poisoning with cyanides or fluorides). One may conceive of the pigment-forming system as functioning in the integrated skin under the handicap of a deficient supply of oxygen, which supply may be augmented by any

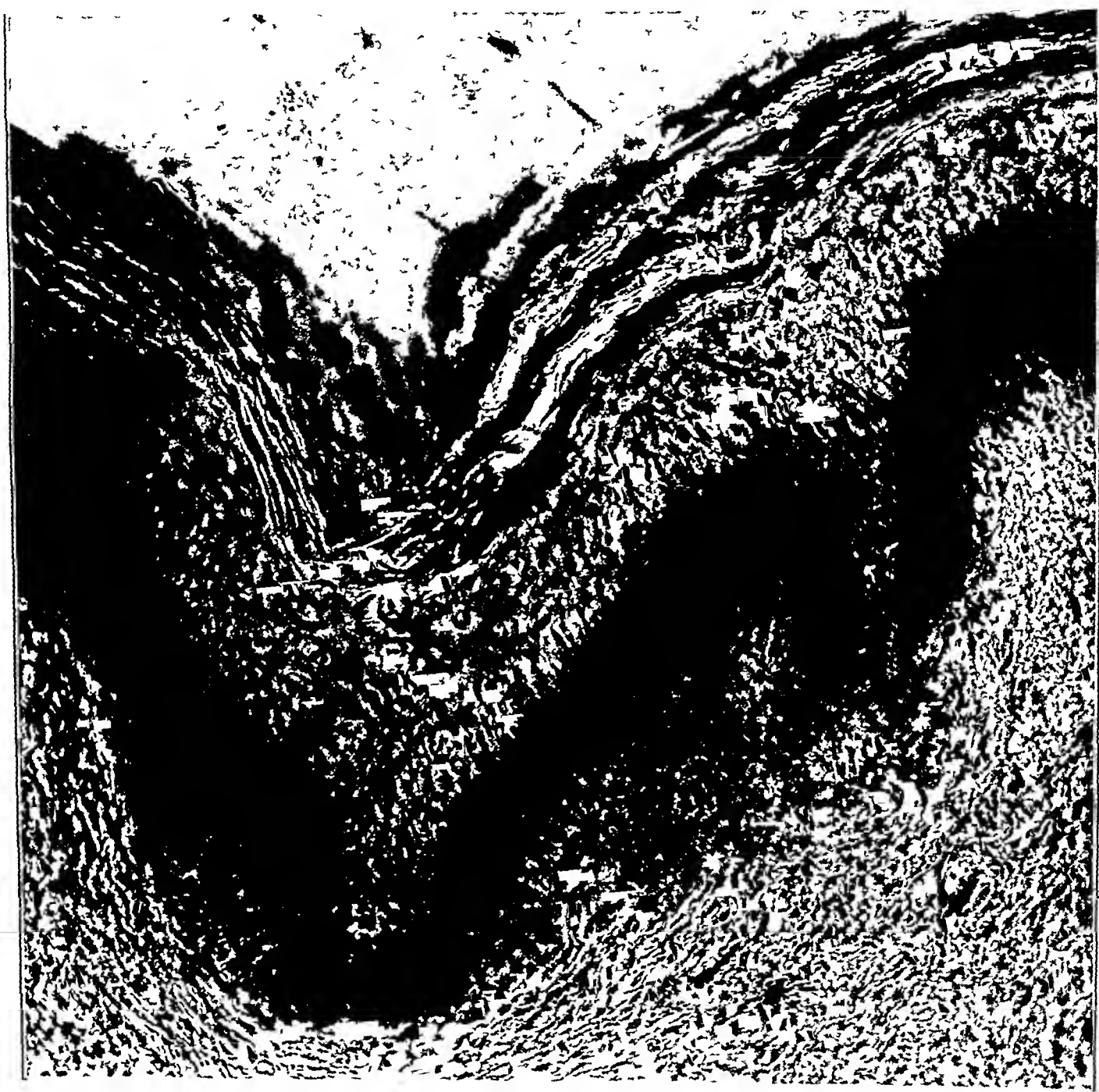


Fig 5—The pigment picture in the epidermis after incubation of the section in 0.1 per cent potassium cyanide solution buffered to  $pH$  9 in an atmosphere of nitrogen

stroying the functional capacity of the cytochrome system of the cell (primary respiratory chain), which system has a primary call on all available oxygen. The damage to the cytochrome system is produced naturally (1) through death (cadaver skin) (2) by moribundity (excised skin) and experimentally (3)

local or systemic change calculated to upset the oxygen balance in the pigment-forming cell. Apparently, ultraviolet rays as a local factor and the aging process as a systemic one can be relied on to produce conditions conducive to increased pigment production.

The adherents to the Bloch theory of melanin production have given the Meirrowsky phenome-

non its most extensive probing. This suggests that an acceptance of the phenomenon apparently offers a forceful challenge to the dopa theory. Essentially, this theory has two indispensable features: an enzymatic process of converting premelanin into melanin and a specific character of the enzyme. Miescher and Minder, in asserting that the Meirrowsky phenomenon is simply an effect of oxygen saturation of melanin particles, tried to sever the phenomenon from

ably strengthened in this belief by the presentation of melanin particles in great number in layers of the epidermis above the basal layer, areas in which new-formed melanin does not physiologically occur. They refused to consider that the many new particles appearing in the basal layer, as revealed by the Meirrowsky phenomenon, might be melanin *de novo* in cells capable of forming new pigment and that there was no inherent contradiction between the acceptance of

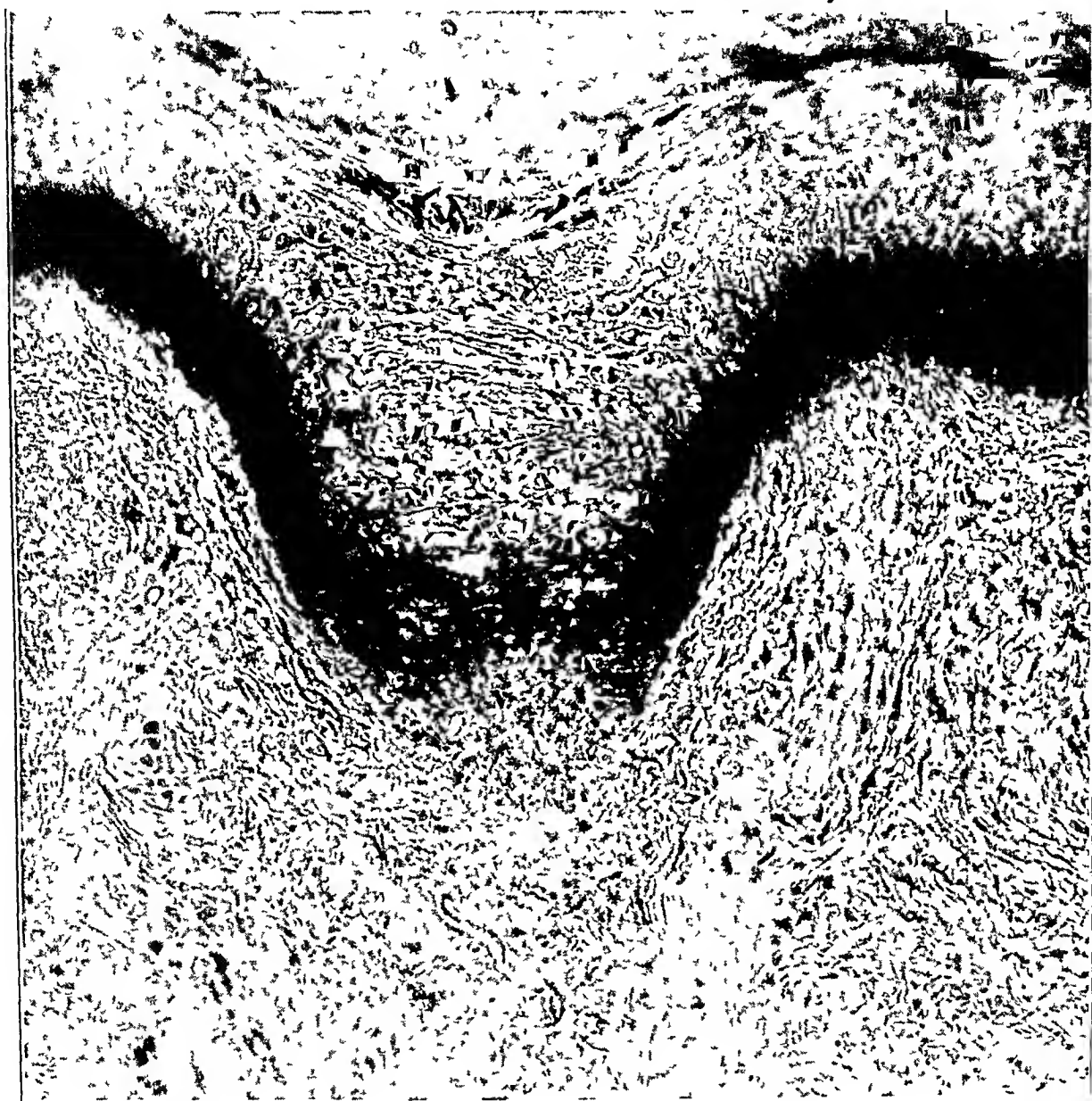


Fig. 6—The pigment picture in the epidermis after incubation of the section in 0.1 per cent sodium fluoride buffered to  $pH$  9 in an atmosphere of air.

the experimental data relevant to the Bloch theory, on the assumed ground that the non-enzymatic process involved could not account for the production of new pigment. They were prob-

ably strengthened in this belief by the presence of melanin in the upper layers of the epidermis and the belief in a new production of melanin in the basal layer under the same experimental conditions.

The explanation of the Meirrowsky phenomenon by a completely nonenzymatic process becomes less tenable, to state it conservatively, if one accepts my reports of the elicitation of the phenomenon in an oxygen-free atmosphere. For under these conditions the

this regard the phenomenon of Meirrowsky becomes another step in solving the problem of the formation of pigment generally and the dopa theory particularly. The Bloch theory has yet to be disproved. Indeed, from many sources confirmation of several of its features

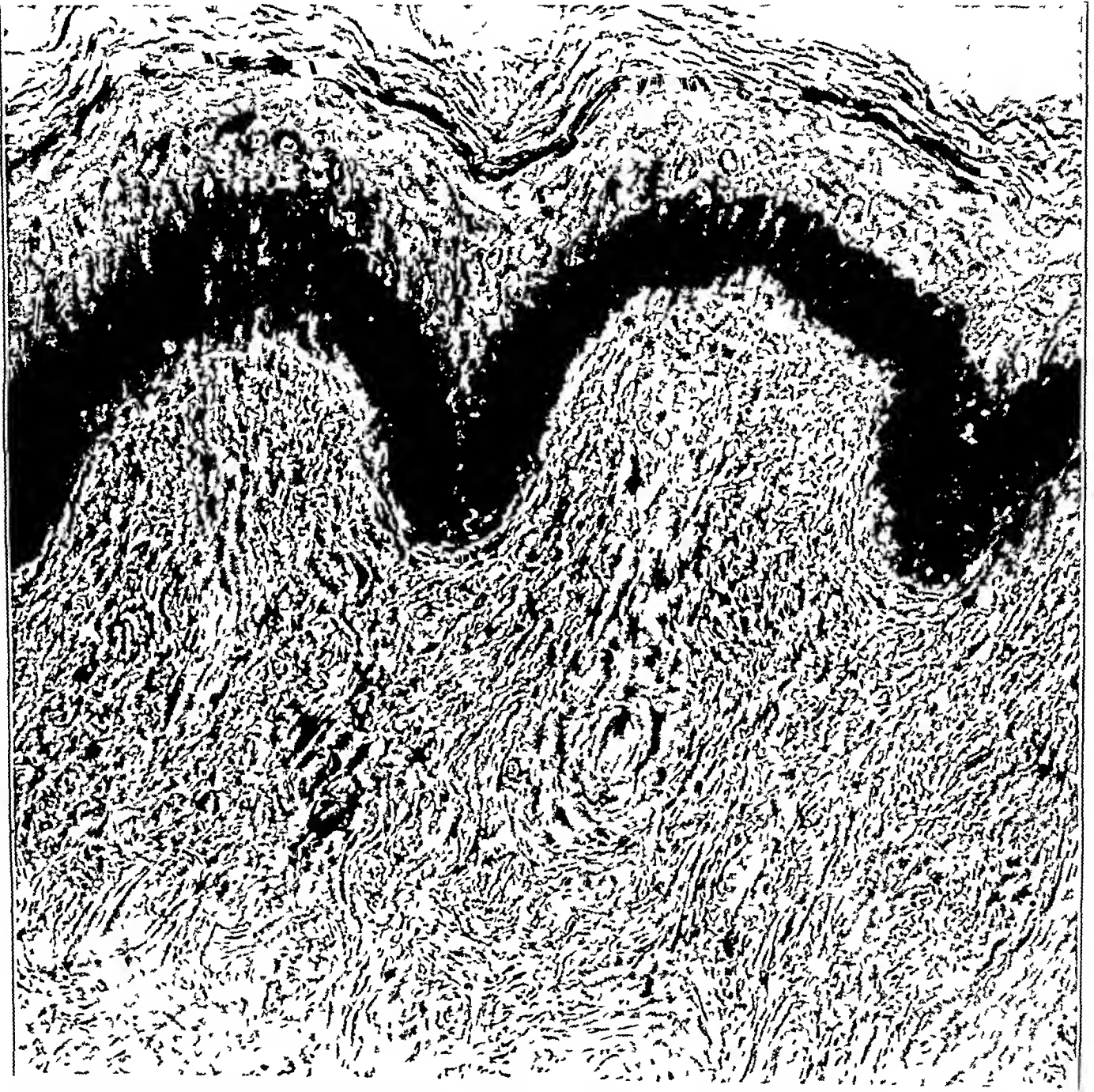


Fig 7—The pigment picture in the epidermis after incubation of the section in 0.1 per cent sodium fluoride buffered to  $pH$  9 in an atmosphere of nitrogen

necessity for an enzymatic process in its production becomes highly probable. Instead, then, of rejecting these data as pertinent to the Bloch theory, I must conclude that they are relevant. In

is established. Further investigation of the Meirrowsky phenomenon may serve to strengthen the Bloch theory rather than to refute it. But first the experimental facts must be amplified



# CUTANEOUS TUMORS OF VON RECKLINGHAUSEN'S DISEASE (NEUROFIBROMATOSIS)

REPORT OF A HISTOLOGIC STUDY, WITH SPECIAL REFERENCE TO  
NERVE FIBERS AND THE BODIAN STAIN<sup>1</sup>

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We wish to report a histologic study of the cutaneous tumors in 15 typical cases of von Recklinghausen's disease (neurofibromatosis) seen in the section on dermatology and syphilology of the Mayo Clinic. The purpose of the study is an attempt to assist in clarifying present conflicting opinions regarding the fibromatous, or neural, origin of these tumors.

This study involves chiefly the demonstration of individual nerve fibers in the tumors. For this purpose, an activated strong protein silver (protargol) stain was utilized. This method, first described by Bodian,<sup>1</sup> is a simple procedure for staining mounted paraffin sections of the central and peripheral nervous systems with reduced silver. It produces uniform, sharp, specific staining of peripheral nerve fibers in contrast to the fainter, grayish purple reticulum and coarser, lighter-staining collagen fibers, which are more readily distinguishable than they are when the usual argentophilic technic is employed. The procedure is as follows:

1 Impregnation with silver. A 1 per cent solution of strong protein silver (protargol) containing 4 to 6 Gm of copper per 100 cc is prepared, and the sections are immersed in this solution for twelve to forty-eight hours at 37 C. The sections then are removed and washed with distilled water.

2 Reduction with hydroquinone. The sections are permitted to stand for ten minutes in a solution of 1 Gm of hydroquinone and 5 Gm of sodium sulfite in 100 cc of distilled water. They then are washed with distilled water.

3 Toning with gold. A 1 per cent solution of gold chloride in distilled water containing 3 drops of glacial

\* From the Section on Dermatology and Syphilology, Mayo Clinic.

This paper is an abridgment, with additions, of thesis submitted by Dr McNairy to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Dermatology and Syphilology.

1 Bodian, D. A New Method for Staining Nerve Fibers and Nerve Endings in Mounted Paraffin Sections, *Anat. Rec.* 65:89-97 (April) 1936.

acetic acid per 100 cc is prepared. Sections are immersed for five to ten minutes in this solution. They then are washed with distilled water.

4 If sections do not have a light purple color, they are placed in a 2 per cent solution of oxalic acid until a purplish tinge appears (usually five to ten minutes). They then are washed with distilled water.

5 Removal of residual silver salts. The sections are immersed in a 5 per cent solution of sodium thiosulfate for five to ten minutes. They then are washed thoroughly in distilled water, dehydrated and mounted in balsam.

Von Recklinghausen's disease is a disease of varied clinical manifestations. The most frequent and almost constant feature observed is the presence of multiple cutaneous tumors, the so-called mollusca fibrosa, which vary exceedingly in extent and size, are irregularly distributed over the skin and show no evidence of localization corresponding to that of the peripheral nerves. In addition, pigmentary disturbances of the skin are numerous and frequently precede the appearance of the tumors in the form of various-sized macules and plaques. There may be tumors of the central and peripheral nervous systems and of the viscera, associated anomalies of the bones and possibly endocrine disturbances. Low standards of physical and mental development in patients with this disease have been reported by Charpentier<sup>2</sup> and other authors.<sup>3</sup>

The gross anatomic characteristics of this condition were first described by R. W. Smith<sup>4</sup> in

2 Charpentier, J. *Maladie de Recklinghausen et psychose periodique*, *Encephale* 2:460-465 (Oct. 20) 1910.

3 Ormsby, O. S., and Montgomery, H. *Diseases of the Skin*, ed. 6, Philadelphia, Lea & Febiger, 1943.  
Levin, O. L., and Behrman, H. T. *Recklinghausen's Disease: Its Elusive Manifestations and Internal Relations*, *Arch. Dermat. & Syph.* 41:480-502 (March) 1940.

4 Smith, R. W. *A Treatise on the Pathology, Diagnosis, and Treatment of Neuroma*, Dublin, Hodges & Smith, 1849.

1849 Virchow,<sup>5</sup> in 1863, was the first to study the tumors in detail. He classified them as true or false neuromas. He said that the true neuromas contained nerve cells and nerve fibers while the false neuromas arose from the connective tissue of the sheaths of the nerves and did not contain nerve cells or nerve fibers. In 1882, von Recklinghausen<sup>6</sup> called attention to the widespread nature of the disease. He contended that the tumors were chiefly fibrous and arose from mature connective tissue of the nerve sheaths. He said that some contained small to large numbers of nerve fibers. In 1910, Verocay,<sup>7</sup> who studied tumors of neurofibromatosis with the van Gieson-Weigert and the Heidenhain hematoxylin and eosin stains, reported the presence of long wavy fibers allegedly nerves, which, he contended, proved that the tumors have a peculiar nerve tissue structure. The cellular elements were assumed to be immature cells of the sheath of Schwann, although he did not report the presence of mature nerve cells in the tumors. He therefore used the name "neurinoma" in an attempt to indicate that the tumors had the structure of nerve tissue rather than of connective tissue. From that time to the present, two schools of thought have developed regarding the origin and nature of these tumors. The theory proposed by Mallory,<sup>8</sup> Penfield<sup>9</sup> and others,<sup>10</sup> namely that the tumors arise from connective tissue, designates the fibroblast as the type cell of these tumors and is based largely on the identification of collagen, fibroglial and elastic tissues, which these investigators considered specific products of fibroblasts. The Schwannian theory, proposed by Masson<sup>11</sup> and

others,<sup>12</sup> which eventuated from the morphologic and cultural studies of experimentally produced "schwannomas" in the cut sciatic nerve of the rabbit, implies that the type cell is of ectodermal origin.

These schools of thought have been formulated largely on the basis of histologic studies of tumors of the peripheral nerves, including those of von Recklinghausen's disease. Microscopically these tumors are similar to other nerve tumors, with an irregularly interwoven reticulated appearance, palisading of the nuclei and whorl arrangement superimposed. Neuro-pathologists generally describe two types of neurofibromas: one the solitary and the other the multiple, the latter type is associated with the other stigmas of von Recklinghausen's disease. Multiple neurofibromas are believed by some authors to differ from solitary neurofibromas histologically and to be a separate entity clinically. Penfield<sup>9</sup> pointed out that axis-cylinders coursed through multiple neurofibromas and that these tumors, therefore, were true neurofibromas. In the solitary tumor, however, the axis-cylinders of the nerve bundle from which the tumor arose were in the capsule and not within the tumor substance, as a result, the tumor was a perineural fibroblastoma. Kernohan<sup>13</sup> said that he had had much difficulty in distinguishing these types of tumors but that as a rule axis-cylinders are encountered more commonly within the tumors of von Recklinghausen's disease than they are within solitary neurofibromas.

The histologic picture of the cutaneous tumors, however, is less definite. They are sharply circumscribed and have a structure distinct from that of the adjacent cutis. They are described as being composed of peculiar nucleated bands and pale, fine, spindle-shaped fibrillae resembling those seen in nerve tissue. Absence of elastic fibers has been noted. The presence of nerve fibers has been reported by some authors but has been denied by others. Gans<sup>14</sup> demonstrated minute nerve fibers in the tumors by using Van

5 Virchow, R. *Die krankhaften Geschwulste*, Berlin, A. Hirschwald, 1863-1867.

6 von Recklinghausen, F. D. *Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuromen*. Festschrift zur Feier des funfundzwanzig-jährigen Bestehens des pathologischen Instituts zu Berlin, Berlin, A. Hirschwald, 1882.

7 Verocay, J. *Zur Kenntnis der Neurofibrome*, Beitr. z. path. Anat. u. z. allg. Path. **48** 1-69, 1910.

8 Mallory, F. B. The Type Cell of the So-Called Dural Endothelioma, *J. M. Research* **41** 349-364 (March) 1920.

9 Penfield, W. Tumors of the Sheaths of the Nervous System, *Arch. Neurol. & Psychiat.* **27** 1298-1309 (June) 1932.

10 Rhoads, C. P., and Van Wagenen, W. P. Observations on the Histology of the Tumors of the Nervus Acusticus, *Am. J. Path.* **4** 145-151 (March) 1928. Bailey, P., and Herrmann, J. D. The Role of the Cells of Schwann in the Formation of Tumors of the Peripheral Nerves, *ibid.* **14** 1-37 (Jan) 1938.

11 Masson, P. Experimental and Spontaneous Schwannomas (Peripheral Gliomas), *Am. J. Path.* **8** 367-415 (July) 1932.

12 Murray, M. R., Stout, A. P., and Bradley, C. F. Schwann Cell Versus Fibroblast as the Origin of the Specific Nerve Sheath Tumor. Observations upon Normal Nerve Sheaths and Neurilemmomas in Vitro, *Am. J. Path.* **16** 41-60 (Jan) 1940. Tarlov, I. M. The Origin of Perineural Fibroblastoma, *ibid.* **16** 33-40 (Jan) 1940.

13 Kernohan, J. W. Tumors of the Spinal Cord, *Arch. Path.* **32** 843-883 (Nov) 1941.

14 Gans, O. *Histologie der Hautkrankheiten, die Gewebsveränderungen in der kranken Haut unter Berücksichtigung ihrer Entstehung und ihres Ablaufs*, Berlin, Julius Springer, 1925, vol. 2.



Gieson's connective tissue stain Friedlander<sup>15</sup> noted, in a single case, nerve fibers running parallel to the blood vessels and crossing and recrossing each other. Kriege,<sup>16</sup> Ehrmann<sup>17</sup> and other authors<sup>18</sup> also mentioned the presence of such fibers. On the other hand, Marie<sup>19</sup> could find no evidence of nerve fibers in the cutaneous tumors removed from a cadaver, al-

though a few were thought to be seen in tumors removed from the patient during life. Gottheil<sup>20</sup> was unable to demonstrate nerve fibers in 3 cases studied, and Anderson,<sup>21</sup> examining a number of histologically representative tumors in a typical case of neurofibromatosis, failed to demonstrate nerve tissue of any kind in the cutaneous lesions. Stout and his associates<sup>22</sup> said, "Many of the

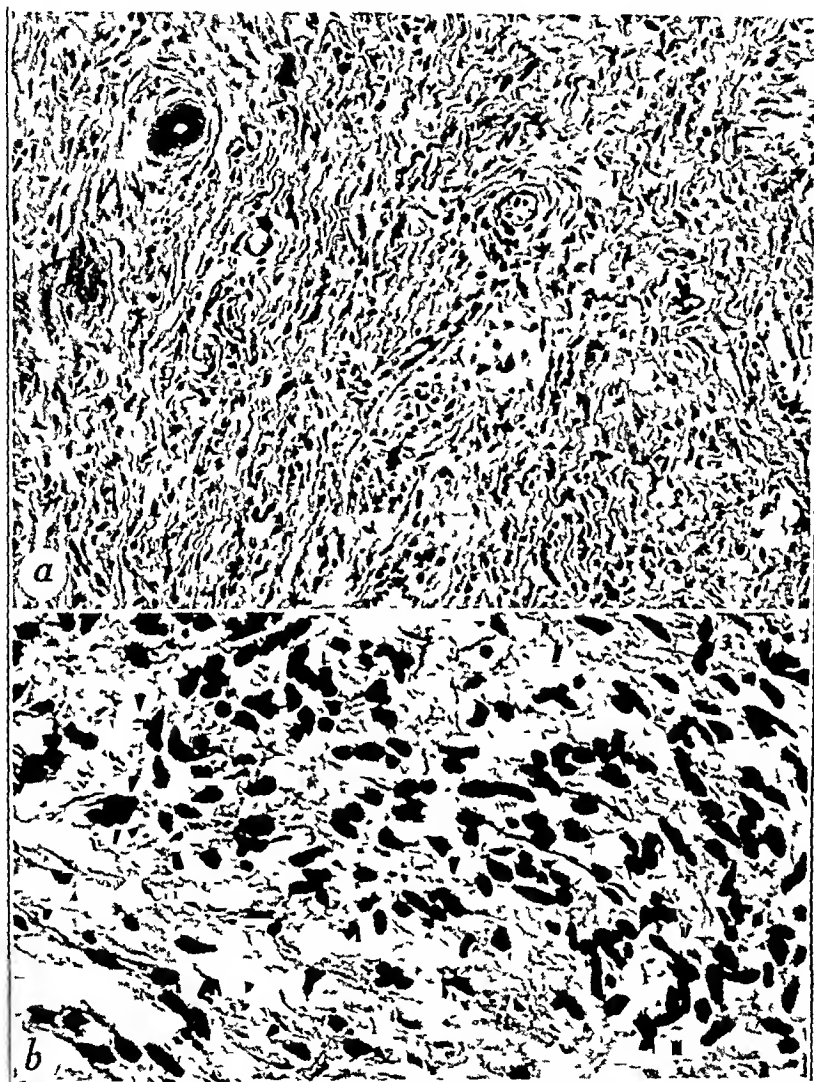


Fig 1—(a) Typical cutaneous tumor of von Recklinghausen's disease in case 1, section stained with hematoxylin and eosin ( $\times 160$ ) (b) Nerve fibers in tumor in case 1, section stained with Bodian's stain ( $\times 420$ )

15 Friedlander, D. Report of a Case of Multiple Neurofibromata, with a Review of the Subject, Based on Two Hundred and Sixty-Two Cases Reported in the Literature, *J Cutan Dis* **28** 497-505 (Oct.) 1910

16 Kriege, H. Ueber das Verhalten der Nervenfasern in den multiplen Fibromen der Haut und in den Neuomen, *Virchows Arch f path Anat* **108** 466-493 (June) 1887

17 Ehrmann, S. Anatomischer und klinischer Beitrag zur Kenntnis der Recklinghausenschen Krankheit, *Arch f Dermat u Syph* **129** 498-515, 1921

18 Ebert, M. H. Recklinghausen's Disease with Demonstration of Nerve Fibers in a Tumor, *Arch Dermat & Syph* **42** 190 (July) 1940

19 Marie, cited by Keen and Spiller<sup>23</sup>

fibromata mollusca, which are such an impressive feature of von Recklinghausen's disease, prove on histological examination to have the morphology of simple fibromata, and a connection with nerves cannot be demonstrated."

20 Gottheil, in discussion on Ravogli, A. Fibromata Molluscum, or Universal Neurofibromatosis, *J Cutan Dis* **29** 79 (Feb) 1911

21 Anderson, L. H. Generalized Neurofibromatosis, with Report of a Case, *J A M A* **74** 1018-1021 (April 10) 1920

22 Stout, A. P., Laidlaw, G. F., and Haagenen, C. D. Tumors of Peripheral Nerves, *A Research Nerv & Ment Dis Proc* **16** 417-439, 1937

## REPORT OF CASES

The cutaneous lesions selected for study included soft, pedunculated papillomatous tumors as well as bluish, domelike ones and, in several instances, pigmented café-au-lait spots. Because of the frequent suggestion by other authors<sup>23</sup> that large tumors might show no evidence of nerve fibers as a result of pressure atrophy or degenerative changes, small ones were selected wherever a choice was possible. Since in several instances the material for study was obtained as the result of excision for cosmetic or therapeutic reasons, tumors of various sizes and ages were included, hence the most desirable specimens were not obtained in all cases. Numerous sections were made of the tumors. In some

We shall report 2 of the 15 cases that form the basis of this report

CASE 1—A white youth aged 18 years had noted the gradual appearance of pigmented macular areas and multiple soft bluish tumors, scattered principally over the trunk, since the age of 9 years. Histologic study of a lesion excised from the right flank revealed a circumscribed oval tumor lying in the midcutis and composed of numerous cells with irregular, elongated, densely staining nuclei and lighter, somewhat granular, ill-defined cytoplasm (fig 1 a). The cells terminated in long, tapering, unipolar and bipolar processes. The arrangement of the cells was irregular, and there was no evidence of the formation of whorls. Between the cells was a spongy, ill defined reticular substance. Throughout the tumor, especially in the outer third,

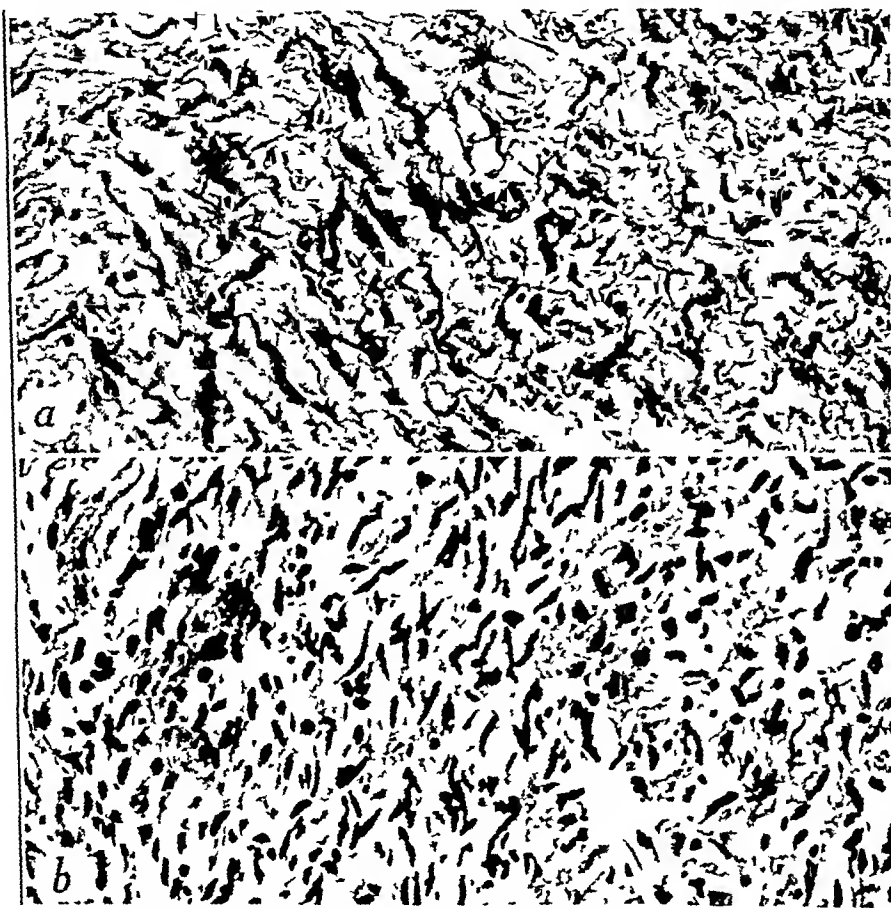


Fig 2—(a) Coarse wavy reticulum fibers (*Gitterfasern*) demonstrated with Maresch-Bielschowsky technic ( $\times 260$ ) (b) Section showing irregular, lozenge-shaped densely staining nuclei, section stained with the Gros-Bielschowsky method ( $\times 260$ )

instances serial sections were studied in an attempt to prove or disprove the presence of nerve fibers. In addition to the Bodian stain, comparative studies were made with hematoxylin and eosin, Maresch-Bielschowsky stain, Gros-Bielschowsky stain and a modification of Masson's trichrome stain (figs 1, 2 and 3). In several cases, Orlandi's stain and cresyl violet also were used.

<sup>23</sup> Keen, W. W. and Spiller, W. G. A Case of Multiple Neuro-Fibromata of the Ulnar Nerve, *Am J M Sc* 119:526-539 (May) 1900. Ravogli A. Fibroma Molluscum, or Universal Neurofibromatosis. *J Cutan Dis* 29:71-78 (Feb) 1911.

were numerous dilated vessels and lymph spaces, nerve bundles and in one area sebaceous glands and sweat glands. The sweat glands were flattened, were separated by the tumor substance and showed evidence of degenerative changes. Individual nerve fibers, densely stained, sharply demarcated, somewhat larger than the cell processes and independent of cell bodies, were readily identified with the Bodian stain in several areas in the tumor substance (fig 1 b). None were identified in association with nerve bundles or dermal appendages.

CASE 2—A married woman aged 42 years presented a typical picture of von Recklinghausen's disease with multiple pigmented macules, "café au lait" spots and cutaneous tumors. A specimen for biopsy was obtained on two occasions. One specimen was obtained from a pigmented plaque in the midscapular region, the other was obtained from a soft bluish tumor which was

bladder-like and readily compressible into a hollow depression in the subcutaneous tissue. Histologically the pigmented plaque revealed little variation from the normal epidermis and cutis other than increased deposits of melanin in the basal layer and in a few dendritic cells in the epidermis. No evidence of nerve fibers or tumor cells could be demonstrated. The other specimen disclosed a typical histologic structure with cellular and reticular components similar to those found in case 1

#### COMMENT ON HISTOLOGIC FINDINGS

The present study was prompted by the conflicting reports in the literature regarding the presence or absence of nerve fibers in the cutaneous tumors. Verocay's<sup>7</sup> belief that the long fibers he demonstrated in the cutaneous tumors were of nerve origin, for example, was contested

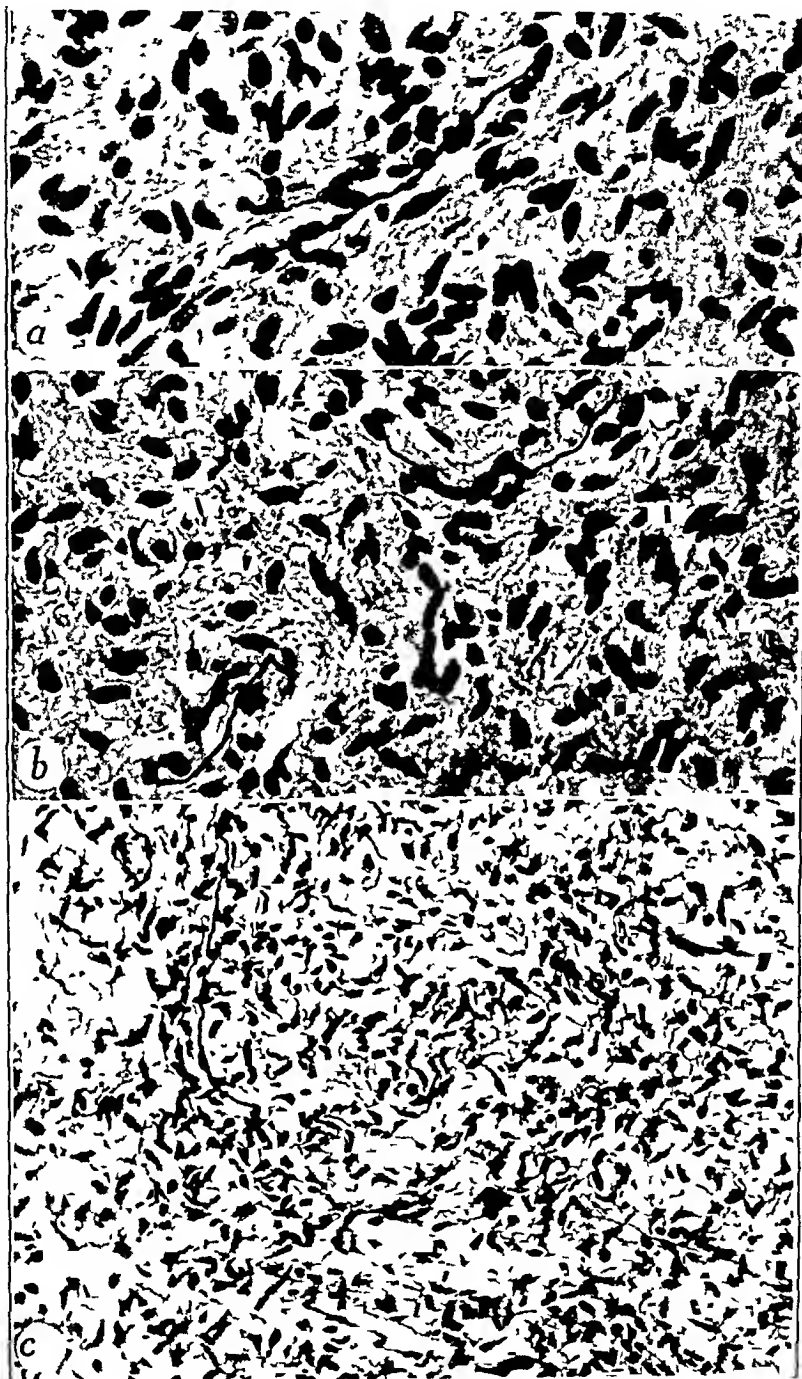


Fig 3—(a) Cutaneous tumor (case 2) containing typical nerve fiber, section stained with Bodian's stain ( $\times 420$ ) (b) Typical nerve fibers, section stained with Bodian's stain ( $\times 420$ ) (c) Numerous coarse, densely staining, irregular nerve fibers and finer, less distinct cell processes and poorly staining reticulum fibers, one may note the apparent association of the fibers with nuclei in several instances, section stained with Bodian's stain ( $\times 260$ )

and a retiform pattern penetrated by numerous dilated vessels and lymph spaces. Short, coarse, deeply stained, wavy nerve fibers were readily discernible in several sites, one near the center of the tumor, another laterally and adjacent to a small vessel (fig 3a)

by Penfield,<sup>9</sup> who by selective staining with silver carbonate demonstrated that they were connective tissue fibers. Most of the studies of such tumors have included only 1 case or, at most,

several cases. Various silver impregnation methods have been preferred by most investigators. Since reticulum fibers stain readily with the usual argentophilic methods, it is conceivable that this might be one source of confusion in the attempts to demonstrate nonmedullated nerve fibers. That the structures are readily distinguished by the Bodian stain is demonstrated by the accompanying photomicrographs (figs 1 to 3).

In each of the 15 cases, nerve bundles were present, usually in the peripheral portions of the tumor. These bundles varied considerably in size and number. Their presence is not adjudged particularly significant from the standpoint of origin of the tumor, since normal dermis and corium are abundantly supplied with nerve structures. In 1 instance, individual nerve fibers were identified in the vicinity of a nerve bundle and extended toward the center of the tumor, thus suggesting their position as finer ramifications of a peripheral nerve. In several cases there were degenerative changes in the nerve bundles, with separation of the individual fibers and partial disappearance of myelin sheaths. These are degenerative changes associated with pressure atrophy, as described by Kurz<sup>24</sup> and other authors.<sup>25</sup>

In 12 cases we were able to demonstrate individual nonmedullated nerve fibers in the cutaneous tumors, generally toward the center of the tumor. They ranged from few to numerous and from short to long and were in all cases characteristic, densely stained and distinct, wavy or irregular and did not run parallel to the tumor cells or their processes. In most instances these fibers were entirely independent of other structures, but in several sections they were contiguous with tumor cells. It was impossible to demonstrate whether this was a definite protoplasmic relationship or whether the structures were merely superimposed.

In 3 cases, many of the tumor cells with large, lighter staining nuclei and exceedingly long, wavy, bipolar and monopolar processes bore a striking resemblance to nerve cells. Cresyl violet was utilized to demonstrate the absence of neurofibrils and Nissl bodies. The processes, which stimulated nerve fibers were finer, were less distinct and stained unevenly, which gave them a granular appearance in contrast to the even,

jet-black appearance of true nerve fibers. Kernohan<sup>26</sup> and other authors<sup>27</sup> have pointed out that degenerating tumor cells can simulate, and sometimes are difficult to distinguish from, nerve tissue. Since specimens in these cases were large, and hence old, and as degenerative changes were noted in some of the dermal appendages and other structures, it can be assumed that the cell processes in question were most likely a part of degenerating fibroblastic tumor cells.

In 3 cases, histologic examination revealed the typical architecture of cutaneous tumors of von Recklinghausen's disease but failed to reveal any structures resembling nerve fibers or cells.

Two cases are of particular interest in that the specimens purposely were obtained from soft, bluish, deep-seated cutaneous tumors. The palpating end of the finger was able to press these balloon-like lesions into and below the level of the skin. This produced the feeling of forcing the soft tumor through a sharply margined ring, as in a ventral hernia. On withdrawal of the finger, the tumors assumed their original size and shape. Clinically, these lesions simulated a condition first reported by Schweninger and Buzzi<sup>28</sup> under the title of "Multiple Tumor-Like New Growths of the Skin." These authors described the insidious onset of balloon-like lesions. Some of the lesions were the color of natural skin, others were bluish or of a slate-tinted hue. In cases of this condition reported by other authors, the lesions have occurred both independently and in association with syphilis. Balloon-like atrophy may appear after the inflammatory lesions of dermatoses such as secondary syphilis, tuberculosis and leprosy. Anetoderma of Jadassohn,<sup>29</sup> while originating as a series of erythematous papules, results in similar atrophic, herniated tumor-like lesions. Clinically, these conditions might conceivably be confused with neurofibromatosis. Chargin and Silver,<sup>30</sup> in a review of the literature on macular atrophy of the skin, said that some of the cases reported by various authors were actually cases of von Recklinghausen's disease. Histologically

26 Kernohan, J. W. Personal communication to the authors.

27 Penfield, W., and Young, A. W. The Nature of von Recklinghausen's Disease and the Tumors Associated with It, *Arch Neurol & Psychiat* **23** 320-344 (Feb) 1930.

28 Schweninger and Buzzi, cited by Chargin and Silver.<sup>30</sup>

29 Jadassohn. Ueber eine eigenartige Form von "Atrophia maculosa cutis," *Arch f Dermat u Syph* **24** 342-358, 1892.

30 Chargin, L., and Silver, H. Macular Atrophy of the Skin, *Arch Dermat & Syph* **24** 614-643 (Oct) 1931.

24 Kurz, cited by Takino.<sup>25a</sup>

25 (a) Takino, M. Ueber die Recklinghausensche Krankheit, besonders ihre Beziehung zu den Hautnerven, *Acta scholae med univ imp in Kioto* **14** 1-15, 1931. (b) Penfield, W. Cytology and Cellular Pathology of the Nervous System. New York, Paul B Hoeber, Inc. 1932, vol 3.

there should be no confusion. The balloon-like tumors of neurofibromatosis are new growths which definitely are circumscribed and have a characteristic architecture. The other diseases have no tumor structure, since they consist essentially of macular atrophy. The Schweninger and Buzzi type of lesions exhibits absence of elastic fibers in the affected regions, a slight increase of these fibers at the margins, round cell infiltration about the superficial blood vessels and dermal appendages and a general picture of cutaneous atrophy. These lesions are distinct from the balloon-like lesions of von Recklinghausen's disease. Anetoderma of Jadassohn shows histologic changes essentially the same as those of acrodermatitis chronica atrophicans, according to the original description, although the infiltrate in the former lies deeper and does not form a border zone between the epidermis and upper parts of the cutis and the rete ridges usually are preserved.

In 2 instances specimens for biopsy were obtained from café-au-lait spots, since some authors<sup>31</sup> have suggested that these pigmented spots may be the forerunners of subsequent tumor development in abortive types. Histologic examination failed to disclose any evidence of tumor cells or nerve structures in the underlying cutis. The sole abnormality consisted of increased deposits of melanin in the basal and dendritic cells of the epidermis.

#### DIFFERENTIAL DIAGNOSIS

Clinical features are usually sufficiently distinctive to enable one to distinguish von Recklinghausen's disease from other types of dermatosis. The histologic picture is characteristic in cases in which the clinical picture might be in doubt. The group of macular atrophies, including tumor-like new growths of Schweninger and Buzzi and anetoderma of Jadassohn, already has been distinguished from von Recklinghausen's disease. Fibroma molle, or cutaneous tags, single or multiple, as well as cutaneous tags of the neck (Templeton<sup>32</sup>) and fibroma molluscum gravidarum (Brickner<sup>33</sup>), all have a similar histologic appearance and are

readily distinguished, since the involved portion of the cutis has an indefinite, loose, spongy, areolar arrangement with a slight decrease in elastic tissue fibers. There is no evidence of neurofibroma. Keloids are usually readily designated grossly. The microscopic picture might be confused with that of a neurofibroma, especially in the earlier lesions, in which cellular elements are more prominent. There are, however, coarse collagenous fibers, arranged in bundles which cross and interweave at various planes, and oval cells with large vesicular nuclei. These cells are not so elongated as the cells of a neurofibroma and they do not stain so deeply with special silver stains. There also is an absence of cell processes and nerve fibers. Neuromas are usually solitary lesions or are few in number. They are tender and firm, have purplish to pink hue, are fixed in the deeper layers of the cutis and are histologically distinctive, with a mixture of fine connective tissue and numerous medullated and nonmedullated nerve fibers. They do not contain neurofibromatous cells. Ganglioneuromas can be readily ruled out by the characteristic ganglion cells, which are not seen in cutaneous neurofibromas. Glomus tumor, in addition to being in most instances a solitary painful nodule usually situated on an extremity, has a characteristic histologic picture with central dilated arteriovenous anastomosis, hyperplasia of epithelioid-like cells and encapsulating nonmedullated nerve fibers in various proportions.

#### SUMMARY

This paper is based on a histologic study of 15 cases of von Recklinghausen's disease (neurofibromatosis). The study involved chiefly a search for nerve fibers with Bodian's method of staining. In 12 cases, nonmedullated nerve fibers were clearly demonstrated. In 3 cases, nerve fibers could not be identified. The presence of nerve fibers in the majority of cutaneous neurofibromas studied is supportive evidence that these lesions are true neurofibromatous structures which arise from the peripheral nerves and their supporting structures and that these nerve fibers are peripheral extensions of the nerve bundles which have been included in the expanding nerve sheath tumors. The cutaneous tumors of von Recklinghausen's disease have a definite histologic architecture and are thus readily distinguished from other cutaneous tumors or from the tumor-like macular atrophy of Schweninger and Buzzi. Pigmented macular lesions seen in neurofibromatosis were studied in 2 cases. No histologic evidence of an underlying neurofibromatous structure or of an increase in nerve fibers could be demonstrated.

31 Weber, F. P. Cutaneous Pigmentation as an Incomplete Form of Recklinghausen's Disease, with Remarks on the Classification of Incomplete and Anomalous Forms of Recklinghausen's Disease, *Brit J Dermat* **21** 49-53 (Feb) 1909. Söldan. Ueber die Beziehungen der Pigmentmaler zur Neurofibromatose, *Arch f klin Chir* **59** 261-296, 1899.

32 Templeton, H. J. Cutaneous Tags of the Neck, *Arch Dermat & Syph* **33** 495-503 (March) 1936.

33 Brickner, S. M. Fibroma Molluscum Gravidarum. A New Clinical Entity, *Am J Obst* **53** 191-199 (Feb) 1906.



# CUTANEOUS DETERGENTS

## EXPERIENCE WITH AN ETHER SULFONATE COMPOUND

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In 1939 a survey was made of 4,500 persons, including physicians, dentists, nurses, students, typists, mothers with young babies, childless housewives, mechanics and others, in order to determine the effect of soap as used in diverse occupations. Analysis of the replies to the varied but definite questions revealed that over 34 per cent of the group gave a history indicating that soap had caused dryness, scaling, itching or burning or some combination of these subjective and objective symptoms. Nurses, dental assistants, surgeons and housewives reported a higher percentage of ill effects from soap than did clerks or typists. About 13 per cent of the persons reporting disturbances were men. Dryness was the most common complaint, and over a third of those reporting dryness also reported associated itching and scaling. By far the most common substitute for soap was some kind of cosmetic cream. Ninety per cent of a group of several hundred persons who reported that they stopped using soap were relieved of symptoms. About 70 per cent of this group resumed its use, and approximately 40 per cent of these reported a recurrence of trouble within a few days or weeks.

Accurate statistical information is difficult to obtain from the subjective reports of patients untrained to evaluate etiologic factors, but it appears from a study of the results of this survey that a substantial percentage of persons have cutaneous irritation from the use of soap.

Many authorities<sup>1</sup> in the fields of dermatology and of industrial medicine state the belief that

1 (a) Schwartz, L. Protective Ointments and Industrial Cleansers, *M Clin North America* **26** 1195 (July) 1942. (b) Klauder, J V, Gross, E R, and Brown, H. Prevention of Industrial Dermatitis, with Reference to Protective Hand Creams, Soap and the Harmful Role of Some Cleansing Agents, *Arch Dermat & Syph* **41** 331-356 (Feb) 1940. (c) Sensitivity to Soap, Queries and Minor Notes, *J A M A* **117** 1662 (Nov 8) 1941. (d) Jordon, J W, Dolce, F A, and Osborne, E D. Dermatitis of the Hands in Housewives, *ibid* **115** 1001 (Sept 21) 1940. (e) Downing, J G. Care of the Skin, *New England J Med* **225** 85 (July 10) 1941. (f) Goldman, L. Patch Test with Soaps, *M Bull Univ Cincinnati* **7** 90 (Nov) 1935. (g) Goldman, L. The Skin Reactions of Infants and Children to Soaps, *J A M A* **108** 1317 (April

the use of soap may initiate, aggravate or prolong a dermatitis and may be a predisposing factor in the development of cutaneous irritation or sensitization from other causes. Some investigators<sup>2</sup> reported their belief that the alkali content is the cause, while others<sup>3</sup> expressed the opinion that the fatty acids commonly present in soap are responsible. A third explanation has been offered,<sup>3a</sup> which is that the irritating properties of the fatty acids are intensified in the presence of alkali and that this is the *modus operandi* in the development of the irritation. A comprehensive study was made by Blank<sup>3a</sup> to determine the effects of soap on the skin. His paper presents data on the action of fatty acids applied to the skin during experiments with controlled hydrogen ion concentrations, and he believed that this action helped to explain how irritation was produced. Although aqueous solutions of the commercial soaps tested showed a pH value of between 10 and 11, he concluded that irritation resulted from neither the fatty acids alone nor the alkali of the soap but from a combination of the two. His studies supplied abundant evidence that the use of soap during treatment of contact dermatitis was inadvisable because, even if the soap was not the etiologic agent, it nevertheless prolonged the irritation after the direct cause was eliminated.

It was reported<sup>4</sup> that the deposition of insoluble soap on the skin also might be provocative of cutaneous disturbance. These deposits result from the combining of the fatty acids, freed by hydrolysis, with the lime salts present in water,

17) 1937. (h) Hazen, H H. Allergic Dermatoses, *Arch Dermat & Syph* **18** 121 (July) 1928. (i) Sulzberger, M B, in discussion on Jordon, Dolce and Osborne<sup>1d</sup>.

2 (a) Mayer, R L. Toxidermien, in Jadassohn, J. *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1933, vol 4, pt 2. (b) Chiego, B, and Silver, H. The Effect of Alkalis on the Stability of Keratins, *J Invest Dermat* **5** 95 (April) 1942.

3 (a) Blank, I H. Action of Soap on Skin, *Arch Dermat & Syph* **39** 811 (May) 1939. (b) Chiego and Silver<sup>2b</sup>.

4 Whitcomb, F C, and Arnold, L. The Relationship Between Acid-Base Equilibrium and Endogenous Bacterial Flora of the Skin, *J Invest Dermat* **4** 317 (Aug) 1941.



especially hard water. Such deposits are resistant to the action of detergents and antiseptics and therefore may harbor active bacteria. According to Jones and Lorenz,<sup>5</sup> "The prevention of calcium soap formation in wash water and its deposition on skin, hair or clothing is an active prophylactic measure against staphylococcal skin infection."

In some instances dryness and scaling may be due not to the composition or the  $pH$  value of a detergent but to its defatting action. Furthermore, certain persons have a low threshold of tolerance to detergents due to the inability of their skin to buffer alkali properly or to excrete normal amounts of sebum. The skin under such conditions may conceivably succumb more readily to the influence of industrial irritants or allergenic substances, such as cosmetics and plant oils.

Soap is defined as a cleansing agent made by the action of alkali on fat or fat acids. All soaps, even neutral soaps, hydrolyze during the process of washing to develop a  $pH$  value in the neighborhood of 10 or 11. However, the normal cutaneous surface has a  $pH$  averaging 5.5.<sup>6</sup> Blank<sup>7</sup> showed that most readings determined with the glass electrode of the Beckman  $pH$  meter were within the range of 4.2 to 5.6.

If the cutaneous surface is tested with the Beckman  $pH$  meter after the use of soap and after rinsing and drying, it will usually be found to have a  $pH$  of from 8 to 10, and, varying with the person, an interval from fifteen minutes to a few hours will elapse before a value within the normal range is established by the physiologic action of the skin.

#### DESIRABLE PROPERTIES OF A CUTANEOUS DETERGENT

Before a discussion of substitutes for soap it is advisable for one to consider the following specifications for a satisfactory detergent.

1 When worked with water it should emulsify and peptize the surface layer mixture of excreted

5 Jones, K. K., and Lorenz, M. The Relation of Calcium Soaps to Staphylococcal Infections of the Skin, *Invest Dermat* 4: 69 (Feb.) 1941.

6 Sharlit, H., and Scheer, M. Hydrogen-Ion Concentration of the Surface of the Healthy Intact Skin, *Arch Dermat & Syph* 7: 592 (May) 1923. Memmesheimer, A. Die N-Ionen Konzentration der Hautoberfläche, *Klin Wchnschr* 3: 2102 (Nov. 11) 1924. Levin, O. L., and Silvers, S. H. The Reaction of the Skin and Its Secretions in Eczema. I. The Hydrogen Ion Concentration of the Skin Surface in Eczema, *Arch Dermat & Syph* 25: 825 (May) 1932. These articles are cited in an article by Draize, J. H. The Determination of the  $pH$  of the Skin of Man and Common Laboratory Animals, *J Invest Dermat* 5: 77 (April) 1942.

7 Blank, I. H. Measurement of  $pH$  of the Skin Surface, *J Invest Dermat* 2: 67 and 75 (April) 1939.

and accumulated fats that have been adsorbed by particles of soil, so that it can be dispersed from the skin by rinsing.

2 It should not interfere with the normal functions of the skin or damage the protective layers of the epidermis.

3 The hydrolyzed product should have a  $pH$  value that corresponds to that of the average normal skin.

4 No undesirable residual layer should be deposited on the skin.

5 It should cause no discomfort and should be pleasurable and agreeable to use in order that physicians prescribing its use may obtain the cooperation of patients.

6 It should produce suds. For some three centuries suds have been a symbol of cleansing efficiency. Suds do assist mechanically in dispersing soil. The development of suds indicates when sufficient detergent material has been applied. Inability to produce further suds is a rough index of the exhaustion of the detergent property. The disappearance of suds after repeated rubbing and rinsing demonstrates the removal of the detergent material.

#### DETERGENTS USED AS SUBSTITUTES FOR SOAP

A variety of agents have been used as substitutes for soap in an attempt to remove soil without producing undesirable subjective or objective symptoms. They may be grouped as follows: (1) water, the greatest value of which is to aid the detergent action of other agents, (2) substances that have an adsorbent action, such as wet cornmeal and colloidal clays, or adsorbent abrasives, such as pumice and sand, (3) materials, such as liquid petrolatum, petrolatum and cosmetic creams, that partially emulsify and detach accumulated fat and soil, (4) so-called neutral soaps, that emulsify, saponify and disperse accumulated fat and soil, (5) superfatted soaps, (6) sulfated oils (commonly but improperly called sulfonated oils),<sup>8</sup> that emulsify fats and when used with water disperse soil, (7) sulfated alcohols, (8) sulfated esters, (9) sulfonated ethers.

8 (a) Lane, C. G., and Blank, I. H. Cutaneous Detergents, *J A M A* 118: 804 (March 7) 1942. (b) Snell, F. D. Surface-Active Agents, *Indust & Engin Chem* 36: 1 (Jan) 1943. (c) Epstein, S., Thronsdon, A. H., Dock, W., and Tanter, M. L. Possible Deleterious Effects of Using Soap Substitutes in Dentifrices, *J Am Dent A* 26: 1461 (Sept.) 1939. (d) Gershenfeld, L., and Witlin, B. Surface Tension Reducents in Bactericidal Solutions: Their in Vitro and in Vivo Efficiencies, *Am J Pharmacol* 113: 215 (June) 1941.

## OBJECTIONS TO THESE SUBSTITUTES

Water only partially dislodges and disperses soil and does not remove soil combined with fats or oils. Materials such as those mentioned in group 2 are poor detergents, causing dryness and epidermal loss. Those in group 3 only partially emulsify the sebum and grease adsorbed by the soil and the resulting mixture can only be partially wiped from the skin. This does not constitute complete or pleasing detergency. Neutral soaps contain fatty acids that may cause irritation and that when hydrolyzed develop a definite alkaline reaction. As with other soaps, when they are used with tap water (especially hard water) insoluble calcium and magnesium salts are formed and deposited on the skin, hair and bathing equipment ("bathtub ring"). Superfatted soaps are subject to the foregoing criticism. Sulfated oils tend to be drying and have been reported to be irritating in an appreciable percentage of cases.<sup>9</sup> Furthermore, they do not produce suds and otherwise are esthetically unsatisfactory.<sup>10</sup> Sulfated alcohols and sulfated esters are good detergents and do produce suds but are objectionable, as are the sulfated oils, because of their drying properties and the irritation that may be produced by the products of hydrolysis. Sulfonated ethers merit special consideration and will be discussed at length in the following section.

## SULFONATES CONTRASTED WITH SULFATES

If a true soluble alkyl sulfate is mixed with water, it will produce sulfuric acid. All the commercial alkyl sulfates tested gave a pH value above 7, but when they were mixed with water the pH drifted to a decidedly acid level. This hydrolysis occurred immediately with most compounds, with others, after hours or days. A true ether sulfonate also gives an alkaline reaction, but the pH value is unchanged when it is mixed with water because hydrolysis cannot take place. In order not to disturb the natural acid reaction of the skin, it is advisable that cutaneous detergents should be active at a pH value corresponding to that of normal skin. Ether sulfonate may be adjusted to a pH of 5.5 by the use of a weak, non-irritating acid, and when such a solution is used for washing the skin or scalp, suds are produced which also have a pH value of 5.5. Therefore, when this detergent material is used on the skin

the surface of which also has a pH of 5.5, it is logical to assume that the normal acid balance will not be altered as it would be by the use of soap.

Most of the commercially available synthetic detergents are true sulfates and contain the hydrolyzable acid sulfate radical. Hence they release small quantities of sulfuric acid on standing or when used. This may be a contributing cause of the irritation reported as having been produced by these sulfated compounds<sup>11</sup>, for if a small amount of sulfuric acid even in extreme dilution is left on the skin this nonvolatile acid becomes concentrated as the water evaporates. Moreover the hydrolysis is accelerated in dilute acid solutions which as stated<sup>7</sup> are present on the skin.

Most if not all of these synthetic agents contain the sulfur joined directly to the oxygen atom and that in turn, to a carbon atom, chemically represented as  $R-O-SO_2-OH$ . An ether sulfonate, however, contains the sulfur joined directly to a carbon atom,  $R-SO_2-OH$ . The latter compound cannot hydrolyze to produce sulfuric acid, as the bond  $R-S$  is extremely strong. This is not true of the weak bond  $R-O$ .

## A SULFONATED ETHER DETERGENT CREAM

During a period of five years in private practice and in the allergy and dermatologic clinics of the Massachusetts General Hospital, a detergent cream,<sup>12</sup> composed of a sulfonated ether, petrolatum, lactic acid and wool fat cholesterol, was used. This stable emulsion has the consistency of a thick dairy cream. It possesses active emulsifying, sudsing and dispersing properties. The surface activity is estimated to be about 40 per cent greater than that of soap.

Because its power to depress surface tension of water exceeds that of soap, this detergent cream is a more rapid and thorough cleanser of the skin including the orifices of the pores and follicles, than soap is.

The cream spreads easily and requires little water to produce lather. Light friction aids emulsification of the resident oils and peptization

11 (a) Biederman, J. B. Sensitivity to Drene Shampoo, *New England J. Med.* **217**:1088 (Dec. 30) 1937. (b) Schwartz, L. Actual Cause of Dermatitis Attributed to Socks, *Pub. Health Rep.* **49**:1176 (Oct. 5) 1934. (c) Osborne, E. D., and Putnam, E. D. Industrial Dermatoses, *J. A. M. A.* **99**:972 (Sept. 17) 1932. (d) Blank.<sup>2a</sup> (e) McCarthy.<sup>2a</sup>

12 This product is manufactured by Fairchild Bros & Foster, New York, under the trade name pHISO-DERM.

9 (a) McCarthy, L. Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, p. 50. (b) Blank.<sup>2a</sup>

10 Sharlit, H. Soap and the "Soap Problem," *New York State J. Med.* **43**:160 (Jan. 15) 1943.

occurs, with subsequent dispersion of the soil into the suds. Rinsing is readily accomplished.

Because of the selective emulsifying power of the ether sulfonate and the emollient property of the preparation, the washing process does not dry the average skin or scalp. Some skins, however, secrete abnormally small amounts of sebum, and for this condition it was found advisable to prescribe the oily type of the cream, which contains about 50 per cent of emollient materials.

The cream itself, as well as the suds produced, has a pH value of approximately 5.5. It contains none of the fatty acids used in soaps and no perfume or coloring matter. It has been shown that (unlike soap, the sulfated oils or the alkyl sulfates) it may be left on the skin, when indicated, for a period of hours without harmful effects.

The detergent is active in hot or cold water, in soft or hard water and in sea water. Soap, of course, is precipitated by sea water, forming curds, few or no suds are formed, and the mixture is ineffective as a cleansing agent. This detergent, however, is not precipitated because compounds are formed which are soluble. Suds are produced, and effective cleansing is accomplished. It is therefore distinctly useful as a routine cutaneous detergent and a shampoo for maritime use. Its use should be valuable as adjunctive treatment of certain casualties encountered in naval warfare, such as immersion in oil. The unsuitability of soap for this purpose is well recognized.

The fact that the cream is a particularly active emulsifying agent for oils of all types explains its adaptability to the needs of industry. It is active under acid, neutral or alkaline conditions of use, and no insoluble soap residues remain on the skin or hair after rinsing.

Extensive use and results of cutaneous tests have proved that it is not a primary irritant and that it is hypoallergenic. Animal experimentation has proved that it is nontoxic and that it is less irritating to the eyes than soap.<sup>13</sup>

#### EXPERIENCE WITH THE DETERGENT

During a period of four years 374 patch tests with the detergent cream were included in a series of 8,628 tests with various allergens applied to several hundred patients with normal or abnormal skin. Positive vesicular reactions to this cream occurred in a fraction of 1 per cent. Approximately the same number of positive reactions to hydrous wool fat and to petrolatum was obtained. Another series of patients, 72, with asthma, hay fever or some form of allergic der-

matitis were tested with this cream, my window patch test method being used.<sup>14</sup> The skin was observed for seventy-two hours, and all tests showed a negative response. The same patients were retested similarly after a two week interval, and negative results were again obtained. This experiment demonstrates that the product has low or no sensitizing properties.

The detergent has been used as a substitute for soap for various periods on over 2,000 persons with normal or abnormal skin. It has been used on the face, hands, scalp and body of infants, adults and aged persons. Some patients complained of a sensation of dryness after using the cream for the first time. This was considered to be due to the fact that they were accustomed to the feeling produced by the mildly keratolytic effect of alkaline soaps. This subjective feeling of dryness was relieved by the substitution of the oily type of detergents. When attempts were made to cleanse exuding, macerated or fissured surfaces, transient smarting sometimes occurred and occasionally aggravation resulted from the cleansing process. Approximately 200 patients have used this cream, excluding soap and all other detergents, for a period of from one to four years without having undesirable subjective or objective symptoms.

#### SUMMARY

Investigators in the field of dermatology and industrial medicine believe that the use of soap may initiate, aggravate or prolong certain types of dermatitis. Analysis of a survey of about 3,500 persons in diverse occupations disclosed that over 34 per cent believed that soap caused dryness, scaling, itching or burning or some combination of these symptoms. Because personal cleanliness is essential to good hygiene and social acceptability and because it usually is an adjunct of dermatologic therapy, it is necessary that a substitute for soap be made available.

In considering the properties of soap and a variety of substitutes for soap that have been used in recent years it is apparent that they do not fulfil all the qualifications of a desirable cutaneous detergent.

A detergent cream, composed of petrolatum, wool fat, cholesterol, lactic acid and a sulfonated ether, has been used for five years in private practice and in clinics of the Massachusetts General Hospital. The detergent lowers surface tension of water considerably more than does

13 Tamter, M. L., and others. Unpublished data.

14 Guild, B. T. Window Patch Test, *Arch. Dermat. & Syph.* 39: 807 (May) 1939.

soap and is an active emulsifier of all types of oil. These properties make the cream about 40 per cent more effective than soap. It is more rapid in action than soap and requires less water and less friction to produce suds. It cannot hydrolyze to form sulfuric acid, as do the soluble alkyl sulfates. It contains no soap fatty acids and no perfume or coloring matter.

The cream, as well as the suds it generates, has a  $p_H$  value of 5.5, which corresponds to that of the average of normal skin. The cream is active

under acid, alkaline and neutral conditions and when used with either hard or soft, cold or hot water. When used with sea water it is a good detergent and produces suds. When used with any of the aforementioned types of water, the detergent leaves no harmful residues on the skin or hair.

The preparation is no more toxic than soap would be if accidentally ingested. It is not a primary irritant. It is hypoallergenic.

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# A SEVERE SYSTEMIC REACTION TO A BEE STING

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LOS ANGELES

Reports on systemic reactions to bee stings are scarce, and the fact that a severe general reaction may develop in the absence of pronounced local inflammation has to my knowledge been emphasized only by Helm<sup>1</sup>. Thus the sequence and location of the cutaneous symptoms in the following report are noteworthy.

On an unusually warm and sunny day in January, while I was walking near the Beach Club of Santa Monica, Calif, in bathing trunks, without shoes, I stepped on one of many half-dead bees, lying in the sand near the water line. I felt a sharp pain on the plantar surface of the left great toe, which abated when I started to walk in the water. About ten minutes later there were tingling and stiffness of the palms, soon followed by numbness and edema of the lips, and by tingling over the scalp, in the axillae and about the genitalia. There was no pruritus at that time, but there was an urgent desire to touch the skin in the involved areas, and light stroking evoked a not unpleasant sensation. These symptoms were followed by generalized cutis anserina. About thirty minutes after the onset of the systemic reaction, malaise and abdominal cramps appeared, by that time angioneurotic edema of the eyelids and the lips was evident, and sharply demarcated, dusky erythema was present around the nasolabial folds, the perioral region and the chin. Within the next half-hour, urticaria, accompanied with intense edema of the prepuce, became manifest in the region covered by the bathing suit and later spread to the trunk. Pruritus was now intense, there was a feeling of tightness around the chest, and abdominal cramps were intensified. Only then did noticeable edema of the left great toe and the anterior part of the left foot develop. Inspection showed only a pin-sized puncture wound on the plantar surface of the toe. A subcutaneous injection of 1 cc of a 1:1,000 aqueous solution of epinephrine hydrochloride, given at the nearest hospital, was followed within twenty minutes by almost complete relief. An hour or two later there was another attack of urticaria, with a recurrence of abdominal cramps and malaise. The symptoms were not severe, but they persisted for part of the following night. The next morning only moderate edema of the left great toe remained, which disappeared during the day.

From the department of dermatology of the University of Southern California

1 Helm, S. Severe Anaphylactic Reaction to Bee or Wasp Sting, *Mil Surgeon* **92** 64, 1943

Inquiry revealed that several members of the Beach Club had experienced general reactions to bee stings in the past, one man was said to have become unconscious a few minutes after being stung. It is supposed that the bees are blown on the beach periodically from nearby Catalina Island. A specimen submitted to the department of entomology of the University of Southern California was classified as *apis mellifica*, the common variety.

The rapid onset of the systemic reaction in my case and the loss of consciousness by the other member of the club are in accord with previously published reports. Helm,<sup>1</sup> von Geldern<sup>2</sup> and Thews<sup>3</sup> have emphasized the rapidity of onset. They have stated that urticaria, lacrimation, asthmatic attacks, localized and generalized edema, quickly ensuing unconsciousness and even a state of severe shock may occur. While there is agreement that individual hypersensitivity must exist, opinion as to the actual causal substance is divided. Benson and Semenov<sup>4</sup> have advanced the belief that sensitivity to protein in the stinger or the body of the bee is the responsible factor in most cases of severe systemic reaction. Gibb<sup>5</sup> has expressed the opinion that the patient may be reacting to pollen adhering to the insect and injected with the sting, a less likely theory.

Bee venom has not yet been successfully analyzed, although it is believed to resemble an albumin or to be of the nature of sapotoxin or cantharidin, consequently, its mode of action is subject to speculation. A logical suggestion has been advanced by Marcou and Derevici,<sup>6</sup> who

2 von Geldern, C E. Systemic Effects Following the Sting of Species of Epyris, *Science* **65** 302, 1927

3 Thews, K. Dangerous Allergic Reactions Following Bee Sting, *Zentralbl f Chir* **63** 2497, 1936

4 Benson, R L, and Semenov, H. Allergy in Its Relation to Bee Sting, *J Allergy* **1** 105, 1930

5 Gibb, D F. Anaphylaxis from Pollen Introduced by a Bee Sting, *Canad M A J* **19** 461, 1928

6 Marcou, I, Derevici, A, and Derevici, M. Distribution of Histamine in Bee and Its Venom. Explanation of Cutaneous Reaction to Stings, *Compt rend Soc de biol* **126** 726, 1937

found that the venom contains histamine, to the action of which the cutaneous symptoms are ascribed. Whatever the nature of the causative substance, the hypersensitivity can be successfully treated by injecting an extract made from the whole bee (Fisher<sup>7</sup>).

<sup>7</sup> Fisher, D. C. Hypersensitivity to Bees Successfully Treated with Whole Bee Extract, *J. Allergy* 5: 519, 1934.

## SUMMARY

A systemic reaction to a bee sting was observed and the occurrence of severe systemic reactions in the absence of pronounced local inflammation was noted. The remarkable sequence of distribution of the cutaneous manifestations—that is, palms, lips, scalp, genitalia and trunk—is thought to be of interest.

2007 Wilshire Boulevard



# LOW POTASSIUM DIET IN TREATMENT OF PSORIASIS

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During the past twenty-five years a great majority of the investigations relating to the cause and treatment of psoriasis have been based on the concept that the psoriatic lesions are a local cutaneous expression of a generalized and constitutional disturbance. The underlying disturbance has been variously considered as owing to faults in metabolism involving proteins,<sup>1</sup> carbohydrates<sup>2</sup> or fats<sup>3</sup>, to vitamin depletion, particularly vitamins C<sup>4</sup> and D,<sup>5</sup> and to endocrine disturbances related to the thymus,<sup>6</sup> thyroid<sup>7</sup> pituitary,<sup>8</sup> gonads,<sup>9</sup> adrenals<sup>10</sup> or pancreas<sup>11</sup>.

The literature is both dogmatic and confusing. Evidence presented in support of each concept is for the most part balanced by reports expressing doubt or outright refutation. Striking "before and after" photographs are presented as visual proof of the benefits of a low nitrogen diet, a low fat diet or the use of adrenal cortex extract. Most of the procedures have failed to withstand general application because, in the main, only

then protagonists have obtained satisfactory results or because the stringency of the therapeutic measures has made their continued use impractical. One observer, for example, reported favorable results from the administration of anterior pituitary extract, adrenal cortex extract and pancreatin and from the use of a low fat and a low protein diet, all being employed in the treatment of the same patient simultaneously.<sup>12</sup> In addition to the problem of making practical use of these various modes of treatment, the psychic factor, which is common to all forms of therapy in psoriasis, has made a critical estimate of their value difficult.

Two schools of thought as to the causation and therapeutics of psoriasis appear to have made much impression in the last decade. The theory of Gruetz and Buerger<sup>3</sup> involves a consideration of faulty fat metabolism and is based on their observation that there is a fasting hypercholesteremia and a disturbance in the fat tolerance curve in psoriasis and that a low fat diet produces amelioration of the psoriatic lesions. Conflicting reports<sup>13</sup> as to the hypercholesteremia have appeared both before and since the original article of Gruetz and Buerger. Moreover, Schaaf<sup>14</sup> and Obtutowicz<sup>14</sup> and LeWinn and Zuger<sup>15</sup> were unable to demonstrate abnormal fat tolerance curves for patients with psoriasis. However, while there is some dissent,<sup>13,14</sup> a majority of the subsequent reports by other authors are in

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14 Schaaf, F, and Obtutowicz, M. *Arch f Dermat u Syph* **173** 200, 1935.

support of the benefits derived from a low fat diet<sup>15</sup> The more recent work with soybean lecithin<sup>16</sup> deals with lipids instead of total fats The results so far appear to parallel those obtained with a low fat diet

The second group of investigations began with Grueneberg's<sup>10</sup> use of adrenal cortex extract in the treatment of psoriasis There have been reported three fairly well established facts which could be interpreted as being indicative of a disordered adrenal cortex metabolism in psoriasis (1) a definite and decided diminution in urinary vitamin C excretion,<sup>17</sup> (2) a decrease in the amount of sulfur excreted in the urine but which may be augmented by feeding ascorbic acid,<sup>17a</sup> (3) an increase in the blood potassium level<sup>18</sup> From these facts may be inferred a relationship between psoriasis and the adrenal cortex, as follows

1 Vitamin C appears to be intimately associated with the function of the adrenal cortex Goldzieher<sup>19</sup> has recently summarized this relationship The concentration of ascorbic acid in the adrenal cortex is greater than that in any other tissue The hemorrhages and degenerative changes which develop in the adrenal cortex in the course of scurvy have been shown to be directly related to the vitamin C deficiency In states of adrenal cortex insufficiency, such as postadrenalectomy, Addison's disease and experimental intoxication with diphtheria toxin, injections of adrenal cortex extract are more effective if combined with the administration of ascorbic acid

2 The adrenal cortex not only is rich in sulfur but appears to have a major role in sulfur metabolism<sup>19</sup>

3 The pronounced loss of sodium and the retention of potassium in adrenal cortex insufficiency are well known Recent reports indicate that adrenal cortex control of the plasma potassium level is of major importance, with the

sodium content of the plasma a secondary factor<sup>19</sup>

Shortly after Gruetz and Bueiger introduced a low fat diet for the treatment of psoriasis, Grueneberg<sup>10</sup> began to publish a series of reports concerning the therapeutic value of adrenal cortex extract for this disease By 1938, after five years' experience with 250 patients, Grueneberg<sup>20</sup> expressed his conviction that adrenal cortex extract is distinctly effective in the treatment of psoriasis However, in the hands of other observers, this form of therapy has not produced uniformly successful results Reports have been favorable,<sup>21</sup> unfavorable<sup>22</sup> or equivocal<sup>23</sup>

The use of adrenal cortex extract is to some degree limited by the rather high cost of this material In order to modify this difficulty, as well as to study the physiologic considerations involved, Incedayi and Ottenstein<sup>21c</sup> enhanced the action of the injected adrenal cortex extract by means of a low potassium diet They reported striking improvement in patients treated by this method

In 1935 Lutz<sup>4</sup> reported definite, although temporary, amelioration of the disease in 3 patients with severe psoriasis after administration of ascorbic acid in large doses Although similarly good results were noted by Volpe,<sup>24</sup> others<sup>25</sup> have failed to observe distinct benefits

Incedayi and Ottenstein<sup>21c</sup> also employed ascorbic acid in the treatment of psoriasis However, they simultaneously prescribed a low potassium diet, attempting by this means to modify the action of the adrenal cortex The good results obtained with this combined therapy led them to state that the unfavorable responses to administration of ascorbic acid alone noted by other observers were due to failure to modify adrenal cortex function They expressed their belief that even better results would be obtained

20 Grueneberg, T, in discussion on Riehl<sup>23</sup>

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25 Welcker, A and Friedrich H *Klin Wchnschr* **19** 565, 1940 Welcker, A *Dermat. Wchnschr* **111** 639, 1940 Goldfarb, A E *Treatment of Psoriasis with Lemon Citrin (Vitamin P)*, Citrin Lemonade and Ascorbic Acid *Arch Dermat & Syph* **43** 536 (March) 1941 Reiss<sup>17a</sup> Schwarz<sup>17d</sup> Madden<sup>22</sup> -, C

15 (a) Gate, J, Chanial, G, Vallet, A, and Humbert, P *Ann de dermat et syph* **9** 465, 1938 (b) Madden, J F *Cholesterol Balance and Low Fat Diet in Psoriasis*, *Arch Dermat & Syph* **39** 268 (Feb) 1939

16 (a) Goldman, L *Cincinnati J Med* **23**:166, 1942 (b) Gross, P, and Kesten, B M *Treatment of Psoriasis with Lipotropic Substances Derived from Foodstuffs*, *Arch Dermat & Syph* **47** 159 (Feb) 1943

17 (a) Reiss, F *Chinese M J* **53** 141, 1938 (b) Ramel, E, and Pidoux, Y *Schweiz med Wchnschr* **67** 38, 1937 (c) Incedayi, C K, and Ottenstein, B *Dermatologica* **84** 330, 1941 (d) Schwarz *Schweiz med Wchnschr* **68** 785, 1938

18 Reiss, F *J Lab & Clin Med* **28**:1082, 1943

19 Goldzieher, M A *The Adrenal Glands in Health and Disease*, Philadelphia, F A Davis Company, 1944

in the treatment of psoriasis with large doses of ascorbic acid, a low potassium diet and injections of adrenal cortex extract employed simultaneously. Since no subsequent report of such a treatment has appeared in the available literature, we have studied a group of patients with psoriasis, in accordance with this procedure.

#### MATERIAL AND METHODS

**Subjects**—Eighteen patients were selected for treatment on the basis of an unquestionable diagnosis of psoriasis, duration of symptoms, previous therapy and response, and willingness of the patient to cooperate closely. In all patients the lesions were well established and in most instances widely distributed. The activity of the latter was mainly acute or subacute. Mildly active arthropathy was present in 2 patients.

**Procedure**—The studies were begun, as far as possible, in November and December 1943 and January 1944 in order to permit full seasonal establishment of the lesions and to obviate the question of seasonal improvement with the advent of summer. All patients were ambulant, and in no case was hospital management instituted. Therapy was begun with the oral administration of 300 mg of ascorbic acid per day for one week, after which, in addition intramuscular injections of adrenal cortex extract (Upjohn) were given in doses of 25 dog units twice weekly. After three to four weeks of this regimen, a low potassium diet was begun. While this was not a weighed diet, the relative size of portions of the various foods was discussed with the patients, as in the management of diabetes mellitus. In order to simplify the diet to assure a daily intake of potassium as close as possible to the optimum of 16 Gm, all foods with a potassium content greater than 0.30 per cent were prohibited (see table). In addition, the patients were encouraged to increase their intake of sodium chloride. In most instances, the ascorbic acid dosage was ultimately increased to 600 mg per day, while the amount of adrenal cortex extract was raised to 50 dog units twice weekly. Patients refrained from other forms of therapy. For the relief of itching and dryness of the lesions an ointment of equal parts of hydrous wool fat and petrolatum was prescribed.

#### RESULTS

There was no instance of maintained improvement in any of our 18 patients. One patient was forced to discontinue treatment after the fifth week because of distressing exacerbations following each dose of adrenal cortex extract. In most patients there was no alteration in the lesions other than the ordinary fluctuations in acuity seen in the course of psoriasis. In patients with arthropathy, no benefits were found as a result of treatment. Photographs were taken in many cases before the inception of treatment. We were unable to note any net change in the severity or extent of the lesions at the time treatment was discontinued.

The most promising result was observed in the case of a 37 year old man whose psoriatic lesions first appeared at the age of 7 years. In this pa-

tient, as in the others, the preliminary week of ascorbic acid therapy produced no change. However, after the first two doses of adrenal cortex extract, the smaller lesions showed distinct blanching at the periphery,

#### Percentage of Potassium Content of Various Foods\*

Food	Percentage of Potassium
Meat extracts	4.16
Lima beans	1.731
Wheat bran	1.217
Prunes, dried	1.030
Potato chips	0.918
Raisins	0.820
Nuts, all kinds	0.550
Spinach, uncooked	0.537
Dates	0.504
Broccoli, edible portion	0.406
Sweet potato	0.397
Oatmeal	0.395
Bananas	0.391
Endive	0.380
Beef (20% protein)	0.338
Lettuce	0.332
Celery	0.292
Pineapple	0.270
Tomatoes, or juice	0.267
Egg plant	0.220
Radishes	0.215
Peaches, fresh	0.214
Currants, fresh	0.211
Bread, whole wheat	0.205
Spinach, boiled and drained	0.200
Grapes	0.197
Onions, uncooked	0.185
Oranges, or juice	0.181
Cottage cheese	0.177
Raspberries, fresh	0.175
Ice cream, commercial	0.163
Bacon or pork	0.163
Blackberries	0.169
Grapefruit	0.161
Buttermilk	0.151
Strawberries	0.150
Squash, summer	0.150
Oysters, large	0.145
Milk, whole	0.143
Cucumbers	0.140
Eggs	0.138
Pears, fresh	0.132
Cornflakes	0.132
Macaroni	0.130
Cream, average	0.130
Apples, fresh	0.127
Jelly made with fruit juice	0.128
Parsnips, boiled and drained	0.125
Cabbage, boiled and drained	0.125
Peas, boiled and drained	0.125
Pineapple, canned	0.125
Beans, string, boiled and drained	0.125
Cauliflower, boiled and drained	0.125
Peaches, canned	0.125
Raspberries, canned	0.125
Lemons	0.123
Watermelon	0.121
Farina	0.120
Sweet corn	0.113
White bread	0.108
Coffee, beverage	0.100
Oysters, small, raw	0.092
Cheese, hard	0.085
Turnips, boiled and drained	0.075
Squash, winter, boiled and drained	0.075
Pumpkin, boiled and drained	0.075
Carrots, boiled and drained	0.075
Asparagus, boiled and drained	0.075
Onions, boiled and drained	0.075
Pears, canned	0.075
Rice, white, raw	0.070
Huckleberries or blueberries	0.051
Margarine	0.048
Farina, cooked	0.040
Tapioea	0.039
Tea, beverage	0.030
Butter	0.014
Mayonnaise	0.007
Sugar, white	0.004

\* From Goldzieher M. A. The Adrenal Glands in Health and Disease Philadelphia F. A. Davis Company 1944 p. 403

while the larger confluent lesions exhibited much less redness than before and a decrease in the thickening. After the fourth dose all the lesions appeared definitely paler, the texture of the skin was softer and the patient reported a lessening of the itching. After the

sixth dose, while a few new lesions appeared on the face and neck at the hair line, the patient stated that he was able to go as long as twenty-four hours without application of the palliative ointment, whereas the itching and burning had previously made application necessary at least every twelve hours. At this time, seventeen days after beginning therapy with adrenal cortex extract, the patient had received a total of 125 units of cortex extract and 7,200 mg of ascorbic acid. There was notable blanching of all major areas with decided thinning of the centers and exfoliation of the scales. During the next two weeks progressive improvement was noted in all areas except the scalp, which continued to itch and scale as actively as before therapy was begun. In the sixth and seventh weeks all improvement ceased and many small new lesions began to appear. By this time, a total of 350 units of adrenal cortex extract had been administered and the patient had taken 16,800 mg of ascorbic acid. At this point the daily dose of ascorbic acid was increased to 600 mg, and the semiweekly dose of adrenal cortex extract was raised to 50 units. For the next two weeks there was no change in the lesions. At the beginning of the tenth week the patient was placed on a low potassium diet, while the daily dose of ascorbic acid was maintained at 600 mg and 50 units of adrenal cortex extract were given twice weekly. Within four days there was striking improvement in all areas, including the scalp. There was little change during the next five weeks, the lesions showing exacerbations and remissions as ordinarily seen in psoriasis treated by other means. In the sixteenth week many new lesions began to appear, the older lesions showed unquestionable progressive exacerbation and treatment was discontinued. An optimistic statement of the patient's condition as the result of therapy with ascorbic acid, adrenal cortex extract and a low potassium diet would be "moderately improved."

In connection with this case report it is interesting to note that the patient had previously been treated with roentgen ray irradiation, ultraviolet irradiation, various ointments (including chaulmoogra oil), intravenous injections of thiamine hydrochloride and a low fat diet. All procedures had been strikingly effective at first but failed to maintain improvement.

#### COMMENT

A review of the literature concerning investigations of psoriasis reveals little which can be accepted as factual. Agreement between the reports which even remotely approach unanimity can be found for the most part in relation to sulfur metabolism and vitamin C metabolism. In their publications Grueneberg<sup>10</sup> and Klauder and Brown<sup>26</sup> are in agreement that the skin of psoriatic patients contains abnormally large

amounts of sulfur. As already noted, a fairly uniform concurrence exists that there is an apparent deficiency in vitamin C excretion in the urine of patients suffering from psoriasis. The work of Reiss<sup>27</sup> reveals a relationship between these two substances in that there is a decreased excretion of both in the urine in psoriasis and that increased vitamin C intake by any route augments not only the excretion of urinary vitamin C but that of urinary sulfur. However, since there is no conclusive evidence that vitamin C therapy, and therefore increased sulfur excretion, ameliorates psoriasis, there is some doubt whether disturbed sulfur metabolism is directly concerned in the causation of psoriasis.

It seems to us that the implication of disturbed vitamin C metabolism as either a specific effect or a cause of psoriasis is fallacious. One of the best recognized functions of vitamin C is its role in oxidation-reduction processes. With the heightened local metabolism in the inflamed psoriatic lesions, it is only reasonable to expect increased utilization and decreased urinary excretion of vitamin C.

It is worthy of note that none of the characteristics of adrenal cortex insufficiency have been described as part of the symptoms of psoriasis. Assuming that minimal adrenal cortex hypofunction exists in psoriasis, the dosage of adrenal cortex extract employed by us, as well as by other observers, should be at least uniformly curative. Instead, there is considerable disagreement as to results obtained. The combined use of adrenal cortex extract, high vitamin C intake and a low potassium diet is a procedure which under ordinary circumstances should be adequate to control frank, although mild, Addison's disease. Using these methods of treatment simultaneously, we were unable to influence the course of psoriasis. We, therefore, do not feel that there is justification for the conclusion that a disturbance in adrenal cortex function exists in this disease.

#### SUMMARY

Eighteen patients with psoriasis were treated with ascorbic acid, adrenal cortex extract and a low potassium diet. We have been unable to observe any definite benefit from this form of therapy.

1351 Devereaux Avenue

136 South Sixteenth Street

27 Reiss F. *Dermat Wchnschr* 105 1418, 1937

<sup>26</sup> Klauder, J. V., and Brown, H. Certain Phases of Sulfur Metabolism of Skin, *Arch Dermat & Syph* 34 568 (Oct) 1936

# CUTANEOUS REACTIONS OF PERSONS WITH ATOPIC ECZEMA TO HUMAN DANDER

## RESULTS OF PATCH TESTS ON SCARIFIED SKIN

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The presence of allergenic activity in human dander has been reported by Van Leeuwen and his co-workers,<sup>1</sup> Keller<sup>2</sup> and Hampton and Cooke<sup>3</sup> and has been discussed several times by Sulzberger. Most allergists, however, have expressed doubt that human dander is allergenic for man.

Human dander is a complex mixture of cornified epidermal cells, sebum, sweat and numerous micro-organisms, as well as various dust particles and other material. In recent studies I<sup>4</sup> presented evidence confirming the existence of an allergen for man in human dander. The allergen investigated was found to be separate and distinct from the allergens in feathers, wool, orris, house dust, cottonseed, karaya gum, bluegrass and ragweed pollen. It was found in dander and hair from the scalp but was not detected in scales of skin from the general body surface or in hair, other contents or inner lining of a dermoid cyst of the ovary. The biologic origin of this allergen has not been determined. Its presence was demonstrated by means of cutaneous reactions in certain patients with atopic eczema. In 9 of 11 adults with this disease urticarial reactions to

scratch tests were obtained, and reagins were demonstrated by local passive transfer.

Because of the reports of Peck and Salomon<sup>5</sup> and Albert and Walzer<sup>6</sup> and the discussions of Sulzberger<sup>7</sup> on transepidermal penetration of protein or protein-like allergens and because of clinical considerations of exposure to dander, it was deemed desirable to perform patch tests. Results of these were positive in 15 of 20 children with eczema. Typical eczematous lesions were reproduced by rubbing human dander on uninvolved areas of the abdomen or back.<sup>4c</sup> In the case of the 9 adults with urticarial reactions to and reagins for human dander, referred to in the preceding paragraph, patch tests were negative. These required further study, a report of which is presented.

## EXPERIMENTAL STUDIES

Dander (dandruff) was combed from the heads of persons with normal scalps, separated from hair, extracted with ether and dried. It was then extracted with 2 volumes of 50 per cent glycerin, and the resulting extract was passed through a Seitz filter. This extract was used for scratch tests in 1:10 and 1:100 dilutions. (The undiluted extract preparation was found to be irritating to all skins tested, including those of persons without atopic eczema.)

For the patch tests human dander was mixed with sufficient petrolatum to make a thick paste (1 part of dander to 1 part of petrolatum). This was spread on a piece of white blotting paper and applied with adhesive tape directly to the skin. But for the exceptions noted later, patches were allowed to remain in contact with the skin for two days. Reactions were read at the time of the removal of the patch, one half hour, one day and seven days later.

Ten patients with atopic eczema were studied. Data for 4 of these persons were included in the first report.

5 Peck, S. M., and Salomon, G. Eczema of Infancy and Childhood, *Am J Dis Child* **46** 1308 (Dec) 1933.

6 Albert, M., and Walzer, M. (a) Contact-Reactions in Atopy. Contact Reactions to Silkworm in Atopic Subjects, *J Immunol* **38** 201 (March) 1940, (b) Contact Reactions in Atopy. Incidence of Contact Reactions with Various Allergens, *J Invest Dermat* **3** 119 (April) 1940, (c) Contact Reactions in Atopy. Contact Reactions in Various Atopic Illnesses, *J Allergy* **14** 437 (Sept) 1943.

7 Sulzberger, M. B., in discussion on Albert and

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1 Van Leeuwen, W. S., Bien, Z., and Varekamp, H. Diagnosis of Diseases for Which Anaphylaxis Is Responsible, *Munchen med Wchnschr* **69** 1690 (Dec 8) 1922, Diagnosis of Anaphylactic Nature of Diseases, *ibid* **70** 604 (May 11) 1923, Skin Tests with Extracts of Dandruff from Human Scalp in Allergic Diseases, *Klin Wchnschr* **5** 1023 (June 4) 1926. Van Leeuwen, W. S., and van Niekerk, J. Positive Cutaneous Reaction Produced in Allergic Individuals by Aqueous Extract of Scales of Human Skin, *Ztschr f Immunittatsforsch u exper Therap* **63** 46, 1929.

2 Keller, P. Relations Between Asthma and Eczema, *Arch f Dermat u Syph* **148** 82, 1924.

3 Hampton, S. F. and Cooke, R. A. The Sensitivity of Man to Human Dander with Particular Reference to Eczema (Allergic Dermatitis), *J Allergy* **13** 63 (Nov) 1941.

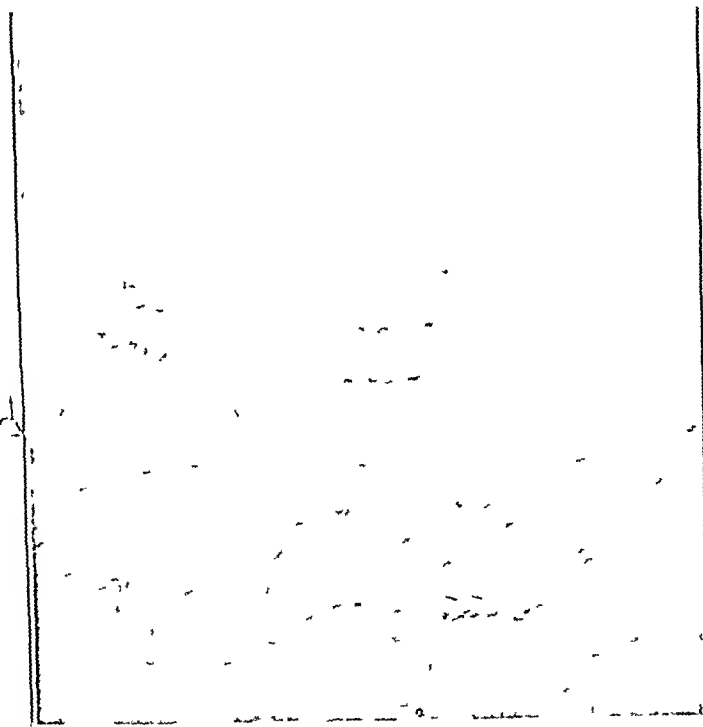
4 Simon, F. A. (a) On the Allergen in Human Dander, *J Allergy* **15** 338 (Sept) 1944, (b) Skin Reactions to Patch Tests with Human Dander, *Ann Allergy* **2** 109 (March) 1944, (c) Human Dander. An Important Cause of Infantile Eczema, *J A M A* **125** 350 (June 3) 1944.

on this subject<sup>41</sup> Six were new patients, who had typical lesions on the face, neck and shoulders, in the cubital spaces and on the forearms. In 2 patients the scalp was involved. In most of these persons the popliteal regions had been involved earlier in life. Seven patients had suffered with the disease since infancy. All gave family histories which were positive for atopy.

Cutaneous Reactions to Human Dander in Patients with Atopic Eczema

Patient No	Age, Yr	Urticarial Reaction to Scratch Test Dilutions		Eczematous Reaction to		
		1:10	1:100	Patch Test on Normal Skin	Patch on Scratch Test	Massage Test
1	21	++	+	—	++	—
2	23	++	±	—	+++	—
3	17	++	+	—	—	—
4	30	—	—	—	++	—
5	18	++	±	—	—	—
6	14	—	—	± (+)	+	+
7	27	—	—	++	+++	+
8	44	+	—	—	++	—
9	21	++	+	+	++	+
10	22	++	+	—	++	—

Routine cutaneous tests elicited urticarial reactions to foods or inhalants or both in 9 of the 10 patients. Six patients had asthma or hay fever or both, in addition



Cutaneous reaction to a patch on scratch test. On the left are shown two superficial scratches which were made on the skin and to which human dander was applied as a patch test. The patch remained in position for two days. The photograph, taken two days after removal of the patch, shows two linear crusts formed at the sites of two shallow, superficial vesicles surmounted on areas of slight redness and swelling. On the right, barely visible, are two scratches of the same depth made at the same time, to which a blank piece of blotting paper had been applied.

to atopic eczema. In the case of the infants and children in whom reactions to patch tests were positive, the allergen evidently reaches the sensitive tissue by direct penetration through the cornified layer of the

epidermis, or through hair follicles or through gland ducts. In the adults, however, in whom results of patch tests were negative (note exceptions mentioned subsequently and shown in the accompanying table) the question arises. If human dander is really an allergenic excitant of atopic eczema in these patients, by what route does the allergen reach the sensitive tissue? An indirect route by way of the blood stream seemed improbable, hence, further attention was turned toward direct applications to the skin surface.

Patch tests were applied to areas of normal skin of the back and allowed to remain in position for two days. Positive reactions were obtained in 2 of the 10 patients (table, patients 7 and 9). By allowing patches to remain in position for seven days 1 additional positive reaction was obtained (patient 6). Mixtures of dander in petrolatum and also in soap solution were massaged into the skin with the end of a blunt wooden applicator. In 3 patients positive reactions resulted. These consisted of papules located at the sites of hair follicles. A third type of test was then applied, namely, a patch on scratch test. Three scratches about 5 mm in length and 1 to 2 mm apart were made in the skin of the back. Bleeding did not occur. A patch was applied immediately on these scratches and allowed to remain in contact with them for two days.

In 9 of the 10 patients eczematous reactions developed at the site of the test. These consisted of papules, vesicopapules, oozing of serous fluid, crust formation, redness and swelling. The papules were located in and immediately adjacent to the scratches. The redness and swelling extended 1 to 3 mm beyond them. The milder reactions consisted in redness and swelling alone, without papules. Desquamation occurred in one to two weeks. The reactions remained visible for one to four weeks. In 10 persons without eczema all of these tests elicited negative reactions.<sup>8</sup>

COMMENT

The occurrence of reactions to human dander applied to previously scratched skin of certain patients with atopic eczema in whom patch tests on uninjured skin produce no reactions is probably due to the fact that the scratches remove the barrier of cornified epidermis. Thus the allergen is permitted to penetrate to the sensitive tissue. In a small percentage of adults and a larger percentage of children<sup>42</sup> with the disease, the cornified layer of epidermis does not prevent penetra-

8 In several instances a very slight erythematous reaction (hardly perceptible) developed at sites of scratches to which the dander had been applied, while no reaction developed at sites of scratches to which a blank patch had been applied. A similar very slight erythema has been observed in several normal, non-eczematous children at sites to which dander had been applied to normal, uninjured skin. There are two explanations for these reactions: (1) that they are a result of a primary irritant which manifests itself not only in the urticarial reactions to scratch and intradermal tests but in the eczematous reactions to patch tests (including patch on scratch tests); (2) that they are manifestations of a slight subclinical hypersensitivity to an allergen in human dander.



tion of the allergen in reactive concentrations. In these persons reactions may be obtained to patch tests on uninjured skin.

The reactions to patch tests, including patch on scratch tests, resemble closely, in their general appearance, development and retrogression, the naturally occurring lesions of the disease. Patients with atopic eczema, like all other persons are exposed to human dander from their own scalps, from the scalps of other persons or from both.

The concept of human dander as an important allergenic excitant of atopic eczema will account for the following clinical characteristics of the disease: (1) its occurrence in infants who are receiving nothing by mouth except human milk, (2) the frequent failure of dietary manipulation to result in healing of the lesions, even in patients whose diets are based on the elimination of foods which give positive urticarial reactions to scratch or intradermal tests, (3) the tendency of the disease to lessen when the patient is in the hospital, (4) the predilection of the lesions for cutaneous areas near the scalp and in infants for areas not covered by clothing, (5) perhaps even the propensity of the lesions to occur on flexural surfaces, such as the cubital space, which may be areas permitting greater penetration of allergen and (6) perhaps also the tendency of the disease to heal and disappear in hot weather, for it appears to be a clinical fact that in hot weather not only is there less dander on the scalp but that which is present is less dry and less easily scattered about. The less frequent involvement of the scalp as compared with other areas must be explained on the assumption that the threshold of reactivity of the scalp is greater than that of other skin areas. Incomplete experiments now in progress indicate that this is actually the case.

The existence of other important causative factors (possibly allergenic excitants?) in addition to human dander is indicated by observation of the following characteristics. In certain patients the massive intense exposure of a given cutaneous area to human dander, produced by a patch test (on normal skin or on skin which has previously been scratched), results in an eczematous reaction of slight or moderate intensity, while on an area only a few centimeters distant a more intense, naturally occurring, eczematous reaction exists. It is illogical in such instances to ascribe the latter eczematous reaction entirely to casual contact with human dander. Nor will the assumption of localized variations in specific skin sensitivity account for the observation, because experiments now in progress indicate that various cutaneous areas of the body (with the exception of the scalp) exhibit relatively minor variations in their eczematous response to human dander.

#### SUMMARY

Ten patients with atopic eczema were tested with human dander. Seven patients had positive and 3 negative urticarial reactions to scratch tests. Eczematous reactions were obtained as follows:

1 Three patients had positive and 7 negative reactions to patch tests on normal skin.

2 Nine patients had positive reactions and 1 a negative reaction to patch on scratch tests.

3 Three patients had positive and 7 negative reactions to massage tests.

The reactions to patch and to massage tests reproduced the typical lesions of the disease. In 10 persons without eczema results of all tests were negative.

322 West Broadway

# Abstracts from Current Literature

EDITED BY DR HERBERT RATTNER

STUDIES ON PALMAR SWEATING JACOB J SILVERMAN  
and VERNON E POWELL, Am J M Sc 208 297  
(Sept) 1944

Silverman and Powell describe an inexpensive and relatively simple technic for study of palmar sweating, especially that which results from emotional, intellectual and sensory stimuli. They point out that palmar sweating is continuous, is practically uninfluenced by outside temperatures and may be evoked by mental stimuli. The palm is one of the few places where emotional sweating takes place, and palmar sweating peculiarly is an indicator of emotional disturbances. The authors report a study of the palmar sweat response of more than 1,100 patients in an army general hospital. Approximately 25 per cent of the patients showed an intense response (as recorded by their technic). In those patients there invariably was evidence of coincidental emotional strain or disturbance of the autonomic nervous system.

THE EFFECT OF CALCIUM PANTOTHENATE AND PARA-AMINOBENZOIC ACID ON GRAY HAIR IN MAN. A STUDY ON A GROUP OF YOUNG AND OLDER INDIVIDUALS. HAROLD BRANDALEONE, ELIZABETH MAIN and J MURRAY STEELE, Am J M Sc 208 315 (Sept) 1944

Brandaleone, Main and Steele report that of 19 elderly persons with gray hair and 14 younger persons, only 2 exhibited a significant change in color of hair after a six to eight month period of administration of large amounts of calcium pantothenate and concentrated yeast. All but 6 were also given paraaminobenzoic acid.

LINCH, St Paul

REVIEW OF 2,144 COURSES OF RAPID TREATMENT FOR EARLY SYPHILIS. E W THOMAS and GERTRUDE WEXLER, Am J Syph, Gonorr & Ven Dis 28 529 (Sept) 1944

The authors started the rapid treatment of early syphilis at Bellevue Hospital in December 1939. The most effective method with mapharsen alone during a period of from five to ten days requires a total dose of over 1 Gm. When it was given in amounts which appreciably exceeded 1 mg per kilogram of body weight on any one day the incidence of arsenical encephalopathy was more than 1 per cent. In the administration of 909 such courses of treatment, each lasting from six to ten days, 3 deaths occurred.

In a series of 1,046 courses of treatment, each consisting of daily injections of mapharsen in doses of about 1 mg per kilogram of body weight and four fevers induced by typhoid vaccine during a ten day period, there were only 3 cases of mild arsenical encephalopathy and no deaths. In a total of 2,144 courses of rapid treatment the incidence of encephalopathy was higher among men than among women.

Results of quantitative serologic tests during and after the administration of rapid treatment suggest that reagin may be produced for varying lengths of time after the spirochetes have been eradicated. In general, the longer a patient has had syphilis the longer it is

before the serologic reaction for syphilis becomes negative.

Of all patients followed for six months or more after treatment, 80 per cent demonstrated results that were considered to be satisfactory. If patients who were retreated are included 85.6 per cent had results that were considered to be satisfactory. The low incidence of positive spinal fluid findings from six months to four years after rapid treatment is encouraging. Neuro-recurrences after rapid treatment have been fewer than after routine treatment.

A few patients were treated according to a plan of therapy devised by Eagle, in which three injections of mapharsen were given each week during a period of from six to eight weeks. Difficulty was experienced in persuading patients to complete the course of treatment and to report regularly, hence the number of patients treated was too small for evaluation.

INTENSIVE CHEMOTHERAPY OF EARLY SYPHILIS. A W NEILSON, L F BLANEY, L J STEPHENS and R W MAXWELL, Am J Syph, Gonorr & Ven Dis 28 553 (Sept) 1944

Four hundred and eighty-seven patients with early syphilis were treated intensively with mapharsen, each receiving from 900 to 1,200 mg during an average period of five days. More than one half of the patients were treated additionally with an insoluble bismuth preparation in an attempt to create a chemotherapeutic regimen of maximum effectiveness. Four fatalities are discussed in detail. The fatality rate of patients treated was 0.76 per cent.

The Kahn reaction became negative after an average of four and three-tenths months in patients who received mapharsen alone and after an average of two and eight-tenths months in patients who received bismuth in addition to mapharsen. Fifteen per cent of all patients observed for five months or longer experienced serologic or mucocutaneous relapse.

Twenty pregnant women were given therapy, 17 of whom were kept under observation until delivery had occurred. Only 2 infants exhibited definite indications of having congenital syphilis and 2 (under 3 months of age) had positive reactions to the Kahn test.

It is the authors' opinion that the rate of complete cure in this group of patients will not be less than 70 per cent.

SYPHILIS IN GONORRHEA PATIENTS AND CONTACTS. N W GUTHRIE, Am J Syph, Gonorr & Ven Dis 28 583 (Sept) 1944

Thirty-one per cent of patients with gonorrhea and 39 per cent of their contacts had or had had syphilis on admission to Johns Hopkins Hospital during a twenty-two month period. One hundred and twenty-eight nonsyphilitic patients with gonorrhea were re-examined for the presence of syphilis during the twelve weeks after admission. Three were observed to have contracted the disease. This relatively low rate at which syphilis develops in patients with gonorrhea does not justify frequent testing of the blood. Patients should

be inspected for the presence of lesions when the necessary observations for gonorrhea are made. Serologic tests for syphilis should be made on their admission to the hospital and at four to six week intervals during the next twelve weeks.

REUTER Milwaukee

**ECZEMA—ALLERGIC DERMATITIS** STEPHAN EPSTEIN, *Ann Allergy* 2 247 (May-June) 1944

In a comprehensive review of recent literature regarding eczema and allergic dermatitis, Epstein cites 123 references. The article should be read in its entirety by every one interested in this subject.

Especially important appear to be the contributions on autosensitization, on sensitivity to human dander, on industrial dermatitis and on the prospect of a nonspecific therapy for atopic dermatitis and perhaps other forms of eczema by the conjugated histamine antigen (hapamine).

**HISTOPATHOLOGY OF ECZEMATOID DERMATOSES** WILBERT SACHS, CHARLES S MILLER and MARCARTH GRAY, *Ann Allergy* 2 289 (July-Aug) 1944

In a histologic study of four types of the eczematoid dermatoses the authors draw the following conclusions:

"1 Contact dermatitis differs from the other diseases by the type of vesicle, little or no acanthosis, and a mild superficial inflammatory reaction.

"2 Neurodermatitis has a nonedematous regular acanthosis, thickening of the walls of the small arteries and a focal cellular reaction.

"3 Nummular eczema has the epidermis and cutis of neurodermatitis, plus an intraepidermic vesicle.

"4 Eczema is not a disease *suu generis* but probably an expression of several diseases having similar findings. It differs from the other three by an extensive cutis reaction involving the capillaries and intense diffuse cellular reactions. There is also an irregular acanthosis, most often with all signs of edema and sometimes with little or none."

SHAW, Chattanooga, Tenn.

**CONTACT DERMATITIS FROM RUBBER GAS MASK** JOE C GILBERT, *Ann Allergy* 2 339 (July-Aug) 1944

Gilbert reports another instance of dermatitis resulting from use of a gas mask. A patch test with the gas mask rubber elicited a positive reaction. A different type of gas mask was suggested for the patient.

**PERLECHE—ITS NOSOLOGIC STATUS** CLARK W FINNERUD, *J A M A* 126 737 (Nov 18) 1944

Perleche should be regarded no longer as a disease entity but rather as an abnormal cutaneous change occurring in the form of an intertrigo of the labial commissures. Probably, therefore, this term should be appropriately modified in use in order to suggest in a specific instance the cause or the nature of the condition which it names. Infectious perleche could apply to the condition when it is considered to be primarily of bacterial or mycotic origin. Malocclusion, or mechanical perleche, might signify the condition (as seen in elderly persons) when it is caused by a mechanical agent, such as ill fitting dentures. Vitamin deficiency perleche could specify the condition when it is of hypovitaminotic or avitaminotic origin. Idiopathic perleche could designate the condition in instances when no causative factors can be determined.

HENSCHL, Denver

**THE INITIATING AND PROMOTING ELEMENTS IN TUMOR PRODUCTION—AN ANALYSIS OF THE EFFECTS OF TAR, BENZOPYRENE AND METHYLCHOLANTHRENE ON RABBIT SKIN** WILLIAM F FRIDFWAID and PRYTON ROUS, *J Exper Med* 80 101 (Aug) 1944

Previous studies of the effect of tar on rabbit skin have demonstrated that the carcinogen acts in two ways. First, it changes normal cells into neoplastic cells, and second, it encourages the multiplication of the latter. Certain other agents cannot initiate neoplastic change but they can stimulate proliferation of normal epidermal cells and can promote the development of hidden entities which otherwise never would have been of any significance. The present studies with rabbits demonstrate that benzopyrene rapidly induces neoplastic changes but has only slight power to encourage multiplication of the neoplastic cells. Methylcholanthrene has somewhat more and tar considerably more of the latter ability. The character of the benign tumors is about the same in each case, but the pure hydrocarbons excite the connective tissues only slightly and furnish a scanty stroma, and the tumors remain small and indolent. Thus, in appraising the action of carcinogens, one must take into account not only the capacity of these agents to induce neoplastic change and to promote, or perhaps suppress, tumor growth but the ability to condition to no inconsiderable extent both the type and the structure of the developing tumor.

LYNCH, St Paul

**A NEW METHOD OF GIVING POTASSIUM IODIDE** W T GARFIELD, *New England J Med* 229 971, 1943

Garfield describes the use of potassium iodide administered in the form of enteric-coated pills, each containing 1 Gm (15 grains) of the drug, in 12 cases of syphilis. This form of treatment is recommended because it does not precipitate gastric disturbances and because it admits of accuracy in determining the dose.

**TROPICAL DISEASES OF THE SKIN** H FOX, *New England J Med* 231 482 (Oct 5) 1944

Five tropical diseases (yaws, pinta, verruga peruana, cutaneous leishmaniasis and leprosy) are discussed with the purpose of emphasizing their increasing importance: (1) to physicians whose practice may include returned veterans who have contracted a tropical disease while in military service, and (2) to medical officers whose responsibilities may include care of native populations in tropical areas.

RONCHESI, Providence, R I

**PENICILLIN IN THE TREATMENT OF EXPERIMENTAL INFECTION WITH BACILLUS ANTHRACIS** F R HEILMAN and W E HERRFELL, *Proc Staff Meet, Mayo Clin* 19 492 (Oct 4) 1944

Fifty-five per cent of mice treated with penicillin were protected against 10,000 times the lethal dose of *Bacillus anthracis*, even when sixteen hours had elapsed between the inoculation and the beginning of treatment. It is evident that infections with *B anthracis* are susceptible to treatment with penicillin.

HENSCHL, Denver

**BRIEF HISTORY OF THE SCHOOL OF ST-LOUIS** ALBERIC MARIN, *Union med du Canada* 73 1285 (Nov) 1944

The history of dermatology and syphilology in France is intimately connected with that of l'hôpital St-Louis in Paris. It is true that other centers, such as those at Montpellier, Toulouse, Bordeaux, Lyon and Stras-

bourg, became famous, but it was the work produced by the Paris school that was most remarkable

L'hôpital St-Louis, founded by Henry IV in 1607, was used at first for patients with plague or other contagious diseases, on certain occasions patients with tuberculosis were admitted. At that time the hospital functioned only intermittently during epidemics. When conditions of health improved, the hospital was closed. There were always more patients than beds, for example, in 1790 four hundred and fifty-three beds contained 700 patients.

The modern period of dermatology began in 1801 with Alibert, who interested himself immediately in diseases of the skin, about which little was known. In 1804 he began his celebrated lectures, which attracted many students and physicians. Alibert was the first professor of dermatology in Paris and established the universal renown of l'hôpital St-Louis for the study and treatment of dermatoses.

Later Bielt first described the epidermic collaret of papular syphilids, Cazenave studied lupus erythematosus and pemphigus foliaceus, Gibert individualized pityriasis rosea, Devergie first described pityriasis rubra pilaris, Bazin isolated fungi and discussed mycosis fungoides and erythema induratum, Hardy simplified the treatment of scabies, Vidal proved that pemphigus neonatorum is contagious, Besnier popularized the use of biopsy, Hallopeau described acrodermatitis continua, Brocq, Sabouraud, Darier, Milian, Lortat-Jacob and Louste carried on varied and multiple researches which advanced the renown of the Parisian school.

A clinical chair of dermatology and syphilology on the *Faculté de Médecine de Paris* was founded in 1880. Alfred Fournier was the first professor, he became universally known because of his remarkable work on syphilis. His book, "Syphilis and Marriage," was translated into many languages. That which immortalized the name of Alfred Fournier was his conviction that tabes and dementia paralytica are syphilitic in origin and that in the great majority of cases these diseases result from insufficient antisyphilitic treatment. Fournier was succeeded by Gaucher, Jeanselme and Gougerot.

It is expected that the war has only temporarily interrupted the brilliant course of French science.

LAYMON, Minneapolis

#### LYMPHADENOMA ITS ETIOLOGY AND ITS SKIN-LESIONS E C WARNER, Brit J Dermat 56 129 (May-June) 1944

Lymphadenoma is essentially a disease of the reticulo-endothelial system which usually manifests itself first in the lymph nodes, subsequently spreads to involve almost any organ in the body and, as a result of multiple lesions in many different organs, usually terminates in death from cachexia.

The author believes that etiologically lymphadenoma stands in an intermediate position between the granulomas and the generally accepted neoplasms.

The cutaneous lesions of this disease are of various types. Pruritus usually starts on the front of the legs or dorsa of the feet or when generalized is most severe in those areas. Herpes zoster is present in approximately 30 per cent of patients during some stage of their disease and usually is not associated with other signs of a lesion of the spinal cord. Papular lesions, especially on the trunk, appear in a small proportion of patients and may become vesicular. Ulceration of the cutaneous surface is seen usually of the suprasternal

and supraclavicular areas or of the upper part of the neck. In addition, generalized erythroderma is a fairly frequent manifestation of Hodgkin's disease.

#### THE RETICULAR TISSUE AND THE SKIN A H T ROBB-SMITH, Brit J Dermat 56 151 (July-Aug) 1944

In considering the eruptions associated with diseases of the reticular tissue, one should distinguish between those that are toxic manifestations and those that are resultants of specific cellular infiltrations. Of the former, purpura almost invariably is secondary to a hemorrhagic diathesis. Another nonspecific lesion is herpes zoster, which is peculiarly common, especially in patients with Hodgkin's disease. Pruritus without a specific lesion also is common in Hodgkin's disease, but in the patients with leukosis it is usually associated with a cellular infiltration and erythroderma.

The specific cutaneous lesions of the leukoses are most common in lymphoid leukosis, and may consist of (1) a diffuse erythroderma with a variable degree of scaling or (2) purplish nodular tumors affecting the face or (3) small nodules usually scattered over the body but sometimes limited to the conjunctiva or eyelids.

In myeloid leukosis specific cutaneous lesions appear much less frequently and usually develop as purplish nodular tumors that may be either limited to the face or widespread over the body.

Monocytic leukemia, the least common form, frequently presents specific cutaneous manifestations. The lesions may appear either as a diffuse eruption of bluish, slightly raised macules or as firm pale nodules deeper in the skin. The lesions may be transient and often may precede the development of the characteristic oral lesions.

In Hodgkin's disease, although symptomatic cutaneous manifestations (such as pruritus, nonspecific pigmentation, herpes zoster) are common, true involvement of the skin is rare. The lesions are usually on the trunk in the form of plaques which become ulcerated.

BLUEFARB, Chicago

#### CONTACT DERMATITIS IN A MORPHINE FACTORY S ERNEST DORE and E W PROSSER, Brit J Dermat 56 177 (July-Aug) 1944

The authors report on nine patients with contact dermatitis, all of whom were workers in a morphine factory. Seven were men (out of a total of the 16 men employed) and 2 were women (all the women employed). The average period between commencement of employment and development of the first symptoms was fourteen and a half weeks.

One patient was engaged in the process of evaporation, crystallization and purification of "Gregory salt" (mixed morphine and codeine hydrochlorides), 3 in the process of separation of alkaloids and purification of separated morphine salt, and 5 in the process of drying, milling and packing of morphine salt.

In practically all of the patients the eruption began as an irritable erythematous dermatitis of the eyelids and surrounding area, sometimes accompanied with severe edema. Other regions often affected were the nape of the neck and the under surface of the chin in women, and the collar region in men. The arms and hands became involved later. In 1 man the scrotum became involved, and in another the dermatitis eventually became generalized. Otherwise the eruption remained limited to the exposed parts of the body (face, neck, arms and hands). The clinical appearance of the eruption varied considerably in different cases. On the

face and neck it was generally diffuse and of typically eczematous contact type, while on the hands it was sometimes like pompholyx. In 1 case it resembled erythema multiforme. Secondary infection occurred in several cases and lichenification of the skin from scratching in 1 case.

It has not been possible to determine the specific sensitizing agent. The involvement first of the eyelids with an edematous and erythematous type of reaction suggests that the irritant is air borne, as fine dust or spray. To support this is the fact that catarrh of the upper part of the respiratory tract occurred in most cases.

#### DIAGNOSIS AND TREATMENT OF LESIONS DUE TO VESICANTS W. E. CHIESMAN, Brit M J 2 109 (July 22) 1944

In a detailed report on the vesicant gases, the author makes the following recommendations:

*Protection* Remain under cover and protect the face with a gas mask. Clothing contaminated by liquid should be removed at once. If the skin is also contaminated the liquid should be removed mechanically and the skin treated with antigas ointment or bleach cream and then washed. Washing with soap and water alone may spread contamination. Antigas ointments are all cutaneous irritants and must be washed off. The antidote for lewisite on the skin is hydrogen peroxide (20 volume).

*Treatment of Skin* Do not use any prophylactic treatment when the skin is showing actual signs of damage, unless the presence of lewisite is suspected by early cutaneous changes. The value of BAL (a secret formula which is said to be remarkably effective in the treatment of arsenic poisoning) is considerable at this stage. Hair should be clipped from the affected areas and the part cleaned with a bland antiseptic. Try to keep blisters intact. Redundant skin should not be removed unless its removal is unavoidable. Apply a sterile oily dressing. Sulfonamide compounds can be used to counteract infection. Any form of coagulant treatment is contraindicated. Never change a dressing unless absolutely necessary. The exudate from lesions caused by mustard gas or by lewisite is innocuous.

#### SOME COMMON PAEDIATRIC PROCEDURES DOYNE BELL, Brit M J 2 157 (July 29) 1944

Among other procedures, the author discusses the treatment of strawberry nevus, maintaining that there is no exception to the rule that nevus which grow rapidly during the early months of life subsequently retrogress and, of their own accord, disappear on the average in about the fifth year.

#### SCURVY A SURVEY OF FIFTY-THREE CASES R. B. McMILLAN and J. C. INGLIS, Brit M J 2 233 (Aug 19) 1944

In a general discussion of scurvy in adults found in an Edinburgh municipal hospital, the authors presented 53 cases of the "bachelor" type, for which they gave three principal causes: first, ignorance, mainly in men, of the need for potatoes and vegetables in the diet; second, apathy, leading to neglect of the same items because they required preparation and cooking; third, poverty, making it impossible to buy the food required for an adequate diet.

The authors feel that more than propaganda is needed for the elimination of scurvy, and it is suggested that local authorities take practical steps toward the provision of clean, cheap lodgings with canteen facilities under discreet supervision.

#### FATAL PURPURA AFTER SULFAPYRIDINE SHELIA SHERLOCK and J. C. WHITE, Brit M J 2 401 (Sept 23) 1944

In reporting a fatal case of acute purpura occurring during a course of sulfapyridine therapy for pneumonia, the authors emphasize the vascular lesions as a basis for its cause. In view of the high mortality, all patients receiving sulfonamide drugs should be watched for extraneous bleeding.

SHAW, Chattanooga, Tenn.

#### SYPHILIS IN PREGNANT WOMEN T. DIXON HUGHES, M J Australia 2 273 (Sept 9) 1944

In a study based on the routine Wassermann and Kahn tests performed on 28,924 pregnant women, 160 had positive reactions, an incidence of 0.55 per cent.

HENSCHEL, Denver

## Correspondence

### IMMUNIZATION THERAPY OF WARTS

*To the Editor* —Dr Hans Biberstein is responsible for a paper, "Immunization Therapy of Warts" (ARCH DERMAT & SYPH 50 12 [July] 1944). In his paper Dr Biberstein quotes me on page 12 as saying "Findlay's statement that warts of one species are not referable to another species was refuted by Frank Schulz and others" (Schulz, F. Experimentelle Uebertragung von Verrucae vulgares vom Rinde auf den Menschen mit ausserordentlich langer Incubation, Deutsche med Wchnschr 34 423, 1908).

On page 15, Dr Biberstein states "Fifteen patients had condylomata acuminata, 9 of the 10 (90 per cent) who could be reexamined were 'uninfluenced', [sic] 7 who received up to fifteen injections were 'influenced'. This refutes the second part of Findlay's statement that extracts of warts have no curative effect in animals of a different species."

Dr Biberstein has obviously not done me the honor of reading my original paper, since the only reference to Findlay is "cited by Rulison" (Warts: A Statistical Study of Nine Hundred and Twenty-One Cases, ARCH DERMAT & SYPH 46 66 [July] 1942).

This omission on Dr Biberstein's part is the more curious in view of the fact that the true reference to my paper is Findlay, G. M. Warts, in Andrews, C. H., Arkwright, J. A., and others. A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1930, vol 7, p 252. The "System of Bacteriology" is, to my knowledge, available in three medical libraries in New York and is a well known standard work.

If Dr Biberstein will take the trouble to refer to my article, he will find no such categorical statements as he attributes to me. On page 257 there is a paragraph, "The Relation of Human and Animal Warts," in which Ullman's results (1923) in producing a papilloma in the vagina of a dog by inoculation with material from a laryngeal papilloma are mentioned, as well as the failure of Serra (1924) to infect laboratory animals with human warts. An account of my own experiments states that "dog warts failed to infect man, rabbits, mice or guinea pigs, as did bovine warts. Human warts were not infective for dogs, rabbits, rats, mice or guinea pigs." At the time my paper was written this was a fair summary of the position, since the experiments of Schulz (1908) are entirely uncritical.

For the second statement which Dr Biberstein attributes to me there is no evidence whatsoever. I have never used extracts of warts in attempting to cure warts in animals of any species and know nothing of their effects.

The paragraph headed "Immunity" in my article on warts, Dr Biberstein may find of interest.

For the sake of scientific accuracy, I should be much obliged to Dr Biberstein if he would draw the attention of your readers to the errors in his paper.

G. M. FINDLAY, Brigadier,  
A. M. S., West African Force

### EPIDERMOLYSIS BULLOSA

*To the Editor* —In their article (ARCH DERMAT & SYPH 47 647 [May] 1943) Franks and Davis described 4 cases of epidermolysis bullosa occurring in soldiers and made the statement that "No case of this type ['a rare hereditary type with the bullae limited to the feet'] has previously appeared in the American literature." This statement of Franks and Davis was in error in that we had previously described such a case in our article "Epidermolysis Bullosa Hereditaria, Report of Two Cases with Extensive Family Histories" (ARCH DERMAT & SYPH 46 419 [Sept] 1942).

Samitz (ARCH DERMAT & SYPH 48 159 [Aug] 1943), Waisman (J. A. M. A 124 1247 [April 29] 1944), Greenberg (ARCH DERMAT & SYPH 49 333 [May] 1944) and Mooney (ARCH DERMAT & SYPH 50 167 [Sept] 1944) apparently had no difficulty in finding and citing our cases, although several other authors omitted citation of our publication, perhaps because they followed the incomplete references of Franks and Davis.

We have thought it worth while to call these omissions to your attention, as this form of epidermolysis is not only of dermatologic and genetic interest but of particular military importance, as shown in our article. Sulzberger and we first called attention to the military significance of this form of eruption of the feet.

MORRIS LEIDER, Lieutenant Commander (MC), USNR  
RUDOLF L. BAEP, MD New York



# Society Transactions

## NEW ENGLAND DERMATOLOGICAL SOCIETY

JACOB H. SWARTZ, M.D., *President*

FRANCIS M. THURMON, M.D., *Secretary*

*Boston, Feb 9, 1944*

### A Case for Diagnosis (Acrodermatitis Continua [Hallopeau]?) Presented by DR. JOHN ADAMS, Boston

M. A., a white woman, a 41 year old secretary, complains of an eruption intermittently affecting the entire body (exclusive of the face) for eight years. At the onset, the skin at the base of the neck anteriorly became red, and the area enlarged rapidly to cover practically the entire cutaneous surface. Pustular lesions appeared, and painful crusts followed. This eruption was accompanied with a low grade fever, malaise and loss of weight. The first attack lasted three months. Subsequent outbreaks occurred three to six times yearly, each attack lasted two weeks to three months. For the past eight months areas have persisted on her right forearm, wrist and forefinger. Previously, the skin had been normal between these episodes, and the patient had experienced good health.

Examination reveals sharply circumscribed plaques of deeply reddened and thickened skin with scattered pustules and large flakes of dry, purulent exudate. These are seen on the extensor surfaces of the arms, on the trunk, particularly along the right lower portion of the thorax, over the hips and on the right leg. The right forefinger is completely involved. On the scalp there are erythematous plaques 1 to 3 cm in diameter covered with a white scale. The toe nails are yellow and hypertrophied. The hands, feet and face are clear.

The urine was normal. Hematologic studies showed hemoglobin content 12 Gm., erythrocytes 5,320,000, leukocytes 12,100 and a differential count of 71 per cent polymorphonuclears, 19 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. Cultures of materials from the crusted areas yielded *Staphylococcus aureus*.

The oral administration of sulfathiazole caused nausea, vomiting and a febrile reaction. Additional therapy has comprised saline baths and use of an ointment of petrolatum and hydrous wool fat.

#### DISCUSSION

DR. BERNARD APPEL, Lynn, Mass. I could not help observing how closely the lesions on the right elbow resemble psoriasis. There is a moderate amount of typical white, silvery light fluffy scales. I did not scratch deep enough to get pinpoint bleeding. This fairly typical area of psoriasis extends directly and almost imperceptibly into that portion which shows the greatest amount of acute inflammation with the closely placed pinpoint pustules. The eruption strongly suggests a diagnosis of pustular psoriasis.

DR. FRANCIS M. THURMON, Boston. The eruption at first glance does not resemble psoriasis. I have never seen psoriasis with atrophy of the subcutaneous tissues, such as is present on the leg of this patient. Early atrophic changes have begun to involve the forearm and wrist.

DR. JOHN G. DOWLING, Boston. The differentiation between these two diseases, acrodermatitis con-

tinua and pustular psoriasis, is difficult. In both entities pustular lesions occur and are particularly well defined on the chest. A distinguishing factor is the involvement of the extremities. "Acro" is the root word meaning "extremity." In acrodermatitis the primary sites of the involvement are the terminal phalanges. I prefer the diagnosis of acrodermatitis in this case to that of pustular psoriasis. The eruption does not have the shiny dry scaly appearance characteristic of psoriasis. I shall be interested to see what happens with administration of sulfapyridine.

DR. FRANCESCO RONCHESI, Providence, R. I. Have any patients with pustular psoriasis been treated with sulfapyridine?

MAJOR EARL A. GUCKLICH, M.C., U.S. How long can one continue to give sulfonamide compounds? Apparently this woman has received this therapy for over six months.

DR. WAITER F. LEVER, Boston. Dr. Swartz and I started treating patients with dermatitis herpetiformis with sulfapyridine in 1939. Two of these patients have been taking from 2 to 3 Gm of sulfapyridine daily for more than four years. Studies of the blood have been carried out at regular intervals, and no harmful effects have been noted.

DR. G. MARSHALL CRAWFORD, Brookline, Mass. This woman has lesions on her trunk as large as two hands, which resemble those on the arms and legs. The skin on her feet, toes and knees shows changes compatible with psoriasis. The toes are not affected in the same way as the fingers. Considering only the involvement of the toe nails one might be justified in considering this psoriasis. However, the picture as a whole strongly suggests acrodermatitis.

DR. FRANCIS M. THURMON, Boston. Dr. McCarthy called attention to the tongue. I wonder if he has anything further to add.

DR. FRANCIS P. MCCARTHY. I observed that this patient's tongue was practically denuded. There was an intensification of the remaining markings. One or two islands of normal papillae lay near the tip and the color was within normal limits. The picture resembled a glossitis totalis. If the dermatologist would look into the oral cavity as a part of the routine examination, he would note many interesting lesions.

Is the blood level of the sulfonamide compound sufficiently high with these small doses of the drug used over a long period of time to be of any real value? There may be established a tolerance to the sulfonamide drug. In such patients an acute hemolytic anemia may rapidly develop. There is an element of danger in the treatment, and a great responsibility is assumed by the dermatologist who continues sulfonamide therapy indefinitely. The patient might consider taking extra tablets independent of the prescribed dose.

DR. C. GUY LANE, Boston. The only comment I wish to make in respect to Dr. McCarthy's remarks is that I fully appreciate the risks and dangers of sensitization and of perhaps serious results associated with sulfonamide therapy. Because of the pruritus, persons with dermatitis herpetiformis lose their appetites, are below par physically and cannot sleep. Since they are relieved by relatively small doses of the sulfonamide drug, I am inclined to go ahead with this therapy and assume whatever risk may be involved. The 2 patients who have been taking the drug for

two years are comfortable, are not troubled by itching and do sleep. I have not been able to find a substitute that will give them the comfort they demand.

**A Case for Diagnosis (Dermatitis Factitia, Dermatitis Medicamentosa?)** Presented by DR JOHN ADAMS, Boston

M S., a white woman, a 27 year old defense worker, complains of an eruption on the thighs and legs of two years' duration. The dermatitis is characterized by exacerbations and remissions at approximate intervals of two weeks. Eight months ago, for several weeks, similar lesions appeared on the neck and arms. On alternate days for the past five years she has chewed Feen-a-mint. Four months ago after a hemorrhoidectomy she avoided Feen-a-mint, and during this period there was a decided improvement in the eruption.

The eruption is characterized by multihued lesions resembling healing ecchymoses. The lesions are of irregular size and shape, varying from 2 to 10 cm in diameter. All areas are slightly raised and tender to pressure. Some are firm, others, soft.

A patch test with phenolphthalein produced no reaction.

DISCUSSION

DR FRANCESCO RONCHESI, Providence, R. I. Why is a diagnosis of dermatitis factitia considered in this case?

DR C. GUY LANE, Boston. The diagnosis was questioned when, during the rounds of the ward recently, the patient gave a history of repeated trauma to one knee. Persistent lesions developed at the site of this trauma. Later additional lesions appeared on the thighs and legs but not on the upper part of the body. Dr. Adams raised the question of trauma from pounding. We had no reason to suspect that these lesions were self-inflicted, but they did appear soon after and at the sites of the trauma. Although there were muhiary lesions which were relatively difficult to explain on the basis of a medicamentosa, it is difficult, on the other hand, to account for these lesions entirely on the basis of trauma. For a long time she had habitually taken Feen-a-mint and when not taking Feen-a-mint had noticed a remission of the lesions. She was given 2 grains (0.13 Gm.) of phenolphthalein, and the reaction was much less severe than I should have expected. The eruption certainly is not as quiescent as it was a week ago. Today the lesions are rounded slightly elevated, and definitely more palpable and erythematous. I am not willing to subscribe to the diagnosis of dermatitis factitia, but the whole matter is certainly not explained by the phenolphthalein.

DR GORGE E. MORRIS, Boston. May I suggest that capillary fragility could be aggravated by phenolphthalein. The lesions resemble a phenolphthalein eruption. A moccasin venom test should be made before and after the administration of phenolphthalein to see if the reaction is intensified by the medication.

DR ALFRED HOLLANDER, Springfield, Mass. I believe that one should call this eruption dermatitis medicamentosa. On palpation the leg presents a band-like swelling which suggests urticaria. A year ago I saw a man who presented bullous hemorrhagic lesions on the dorsa and palms of the hands. These bullous lesions suddenly disappeared and four or five months later typical urticaria developed, which could not be controlled. Last week I learned that after discontinuing all medication he was completely relieved. Perhaps an allergy or a sensitivity to certain drugs should be considered in such cases.

DR JOSEPH GOODMAN, Boston. It seems to me there are certain aspects of this case which strongly suggest

an atypical form of erythema nodosum, such as the color changes, the persistent eruption, the tenderness and the limitation to the legs. A biopsy might be enlightening.

DR WILLIAM P. BOARDMAN, Boston. For my own information, I should like to know if this patient was given a patch test with phenolphthalein.

DR JACOB H. SWARTZ, Boston. I am aware of the report of Dr. Wise and Dr. Sulzberger on patch tests for fixed eruptions (ARCH. DERMAT. & SYPH. 27:549 [April] 1933), but I thought that such a test might be worth trying in this case, since the eruption is not purely fixed but is a mixed eruption.

DR JOHN G. DOWNING, Boston. Dr. Sulzberger stated that a patch test with phenolphthalein is useless in diagnosing a dermatitis due to phenolphthalein. He does mention the fact that it is only in the eczematoid eruptions of dermatitis medicamentosa that the patch test is of value.

DR ALFRED HOLLANDER, Springfield, Mass. I have never seen a phenolphthalein test produce swelling which penetrates the deeper tissue. Often this type of dermatitis medicamentosa is a fixed eruption.

DR FRANCIS M. THURMON, Boston. In palpating these areas which apparently were ecchymotic, I noticed thin lines, which were slightly beaded as though there might possibly be a low grade inflammatory reaction in the veins or lymphatics. I suggest that the biopsy be deep enough to include the underlying vessels. I suspect that these lesions are connected with the vascular supply.

**Necrobiosis Lipoidica Diabeticorum** Presented by DR LEON BABALIAN, Portland, Maine

This case was presented by means of a case history and colored lantern slides.

D. N., a white American salesman aged 29, complained of a lesion on the front of the right leg of four years' duration.

He had been known to have diabetes mellitus since 1934. Since that time he has had continuous insulin therapy but has not always adhered closely to his prescribed diet. The cutaneous lesion appeared first in 1936 and has been slowly progressing.

Examination reveals a well defined oval plaque 5 by 11 cm., of a pinkish yellow color with erythematous border. The plaque is generally depressed except for its margins which are slightly elevated. Telangiectases are present. In the center of the plaque is an irregular necrotic ulceration 2 by 4 cm. The entire lesion is firm and painless.

The urine was normal. The blood sugar was 110 mg. and the blood cholesterol 166 mg. per hundred cubic centimeters.

DISCUSSION

DR C. GUY LANE, Boston. I should like to say a word here about the lifelike qualities of that Kodachrome still projection. I was almost afraid to touch the picture lest I might rub off some of the serum on my finger. It offers a prospect for teaching and demonstrating cases which would be valuable in the absence of the patient. I wish to congratulate Dr. Babalian.

DR LEON BABALIAN, Portland, Maine. Necrobiosis lipoidica diabeticorum has been described since the advent of insulin. The general belief is that this entity is related to uncontrolled diabetes. The case presented today is especially interesting because the condition appears in a person with diabetes who has been treated with continuous insulin therapy. In spite of this therapy, the disease has progressed.

On the other hand, it is interesting to note that hepatic and arterial manifestations of fat dysfunction are found with greater frequency in cases of diabetes since the advent of insulin therapy (Dragstedt, L R. The Present Status of Lipocair, *J A M A* **114** 29 [Jan 6] 1940). I think that this also has a dermatologic application in that necrobiosis lipoidica diabetorum should be treated not with insulin but with lipocair.

DR C GUY LANE, Boston. One point occurred to me which I neglected to mention, namely, that the ulceration has been present for three months. There is an open ulceration which I estimate to be 3 cm in diameter, perhaps even slightly larger. The inner border appears somewhat infiltrated. It is known that scar or atrophic tissue is apt to be present, and I wonder whether in this instance an excision and skin graft should be done, especially if that ulceration persists. I do not know of nor have I seen anything in the literature with regard to excision of necrobiotic lesions. If the lesion persists or becomes enlarged, the possibility of cancer should be considered.

DR JACOB H SWARTZ, Boston. From what part of the lesion was the biopsy specimen taken? Was it taken before the ulceration appeared?

DR LEON BABALIAN, Portland, Maine. The biopsy was made when the ulceration was present, and the specimen was taken from the border of the plaque.

#### Herpes Gestationis Presented by DR JACOB H SWARTZ, Boston

E B, a Polish-American housewife aged 37, presents an eruption of eight weeks' duration.

In early December 1943, during the seventh month of her fifth pregnancy, erythematous papules accompanied with intense itching appeared on the midflexor portion of her thighs. During the following weeks papules appeared and coalesced on the arms, calves and trunk. By late December vesicles appeared on the thighs and rapidly increased in size to form bullae 1 to 3 cm in diameter. The intense itching could not be controlled. By early January a few of the bullae became hemorrhagic, and additional bullae appeared over the ulnar portions of the arms. In late January the patient delivered a live healthy boy, and after the delivery the eruption completely disappeared.

Examination during the eighth month of pregnancy revealed patches of thickened erythematous, lichenified and excoriated skin on the flexor surfaces of the thighs and forearms. Papules were scattered over the calves, arms and trunk. Large bullae, 1 to 3 cm in diameter, were clear or hemorrhagic, heavily crusted lesions were present on the thighs and forearms.

The laboratory findings prior to delivery were irrelevant.

Treatment comprised denuding the bullae and applying a 2 per cent solution of basic fuchsin to the denuded areas. A calamine lotion also was applied. Over a ten day period she was given sulfapyridine 3 Gm daily.

#### DISCUSSION

DR JACOB SWARTZ, Boston. This patient did not respond to sulfapyridine as favorably as other patients with dermatitis herpetiformis who have been treated with this drug.

DR WALTER F LEVER, Boston. A few years ago, a patient with a generalized bullous eruption was seen at the Massachusetts General Hospital. The eruption had begun in the fifth month of her pregnancy and persisted until shortly after delivery. It was indistinguishable from pemphigus. Pemphigus-like eruptions occur in

pregnancy. They have been described sometimes under the name of pemphigus and sometimes under the name of herpes gestationis.

DR LEON BABALIAN, Portland, Maine. I think the difference between pemphigus and herpes gestationis is that in the latter the vesicles or bullae are arranged in clusters. The case presented today is described as showing clustering of the lesions, such as is present in herpes gestationis. That is quite different from pemphigus.

DR JOHN G DOWNING, Boston. At St Elizabeth's Hospital, Brighton, I frequently see patients who have been treated for scabies. They present a grouped vesicular eruption and at times show bullae. At the present time I am attending a multipara six months pregnant, who for the past two months has shown vesicles and bullae which completely cleared within ten days. A generalized urticaria then developed. After the involution of this eruption, there developed on the flexor surface of one arm a large patch, 5 by 20 cm, which was elevated and flat and composed of pea-sized vesicles. I gave her a simple local application and requested that she report the progress of these lesions. She reported that they disappeared. They had dried and desquamated. In this syndrome, one may see all types of eruption, varying from urticaria to the bullous type of erythema multiforme.

DR JACOB H SWARTZ, Boston. When I saw this patient soon after she delivered an 8 pound (3,630 Gm) infant the eruption had disappeared except for faint blotches marking the sites of previous lesions. The clinical picture coincided with Dr Downing's description. The lesion in this case was of the bullous type, which continued to develop up to the time of delivery.

DR JOHN G DOWNING, Boston. I saw a woman at the Boston City Hospital who had a severe bullous eruption of herpes gestationis. She was advised never to become pregnant again. However, she has had two more babies. In neither of these two pregnancies did she have any disturbance of the skin. Herpes gestationis does not necessarily recur during subsequent pregnancies.

DR JACOB H SWARTZ, Boston. This woman is a multipara, and this is the first time she has had herpes gestationis.

#### A Case for Diagnosis (Acquired Localized Trichorrhexis, [Trichoclasia], Keratosis Pilaris?) Presented by DR FRANCESCO RONCHESE, Providence, R I

A N, a white American girl aged 16 presented a disturbance of the scalp of three years' duration.

She first noticed on the vertex of the scalp several round areas of thinning which were not clearcut spaces of alopecia areata. The hairs in these areas became stiff and coarse and broke off approximately 1 inch (2.5 cm) from the scalp. The hairs on the affected areas have remained in this condition, while the surrounding hairs of the parietal, occipital and frontal portions are of a normal wavy silky texture. She says that she has neither pulled nor cut the hairs.

Examination reveals three distinct types of hair. First, the hair along the frontal, temporal and occipital region appears normal. Second, the hair in the affected areas is sparse and coarse. A moderate degree of fragility and no twists, constrictions, nodes or other alterations are found in the shaft. The roots are definitely abnormal, they are pointed and twisted. No fungi were found on direct examination of the hairs. Third, the hair between the involved hair and the normal hair is coarse, long and kinky. The hairs may be pulled from

the alopecic areas without causing pain. The distal ends of the hairs are smooth, as though cut with shears. There is pronounced keratosis pilaris in the area of alopecia of the scalp and on the arms and legs. The skin of the calves and ankles shows a mild degree of ichthyosis.

value of 94 micrograms of carotene and 88 U S P units of vitamin A per hundred cubic centimeters of serum. The nonprotein nitrogen was 36 mg, the cholesterol 170 mg and the sugar, 93 mg per hundred cubic centimeters of blood. The hemoglobin content was 71 per cent, erythrocytes numbered 5,100,000 and leukocytes



Acquired localized trichorrhexis (trichoclasia) (A) Apparently normal hair on the frontal hair line and back of the head. Low power photomicrograph of an apparently normal section from the back of the scalp. (B) Area of alopecia, keratosis pilaris and spontaneous breaking of the hair at short distance from the scalp. Thin, fragile hair with pointed and twisted roots. Low power photomicrograph from the alopecic area showing a thin and wavy epidermis, hyperkeratosis, indentations and absence of atrophic coil and sebaceous glands.

Cultures planted on Sabouraud's medium failed to yield fungi. The Hinton and Kahn reactions of the blood were negative. The blood showed a fasting

5,400 with a differential count of 68 per cent polymorphonuclears and 32 per cent lymphocytes. The urine was normal.

A specimen for biopsy was removed from the vertex of the scalp and from the occiput. The skin of the occiput showed normal epithelium and normal coil and sebaceous glands. The skin from the vertex showed a thin and wavy epidermis with hyperkeratosis and indentations, as seen in keratosis pilaris, the sebaceous and coil glands were absent or very small. This section in toto was fragmented and showed more friability under the cutting knife than is normal. The ensemble is consistent with a form of atrophy of the skin and its appendages.

NOTE—On June 9, 1945, after fourteen months of intensive vitamin A therapy, although the keratosis pilaris has improved, the area of alopecia of the scalp has not changed.

#### DISCUSSION

DR LEON BABAIAN, Portland, Maine. I could not see nodules on the hairs. Are you sure that it is not a question of simple trichotillomania? It would be difficult to extract the hair forcibly in large quantities. Usually trichorrhoeis is limited to the parietal areas.

DR J. HARPER BLANDFILL, Boston. I suggest the diagnosis of trichotillomania. In the cases that I have observed it occurred in adults who did not deny this vicious habit. Most persons with trichotillomania say there is an irresistible desire to pluck the hairs, this admission is an indication of their desire to be helpful.

DR JOSEPH GOODMAN, Boston. I think that a feature of this girl's history which is of interest is the fact that the lesions she presented on the arms and legs appeared at the same time that her hair started to fall. I note that vitamin A in large amounts is to be administered. I suspect that it may be helpful for the cutaneous lesions and for the hair. I have been impressed by the fact that in certain cases of vitamin A deficiency, there may be a loss of hair.

DR GEORGE E. MORRIS, Boston. The association of keratosis pilaris and monilethrix is well known. The eruption on the girl's arms is characteristic of keratosis pilaris. Therefore, hairs should be carefully and repeatedly examined for beading. It is well known that such beading may be localized to one or several spots of the scalp and also that remissions and exacerbations of the abnormality may occur.

DR FRANCESCO RONCHESI, Providence, R. I. The few hairs from the alopecic area that I had the opportunity to examine showed abnormal roots and fragile shafts. There were no nodes as in trichorrhoeis nodosa. The hairs of the back of the head were apparently normal. This and the fact that the alopecic area is not on the temples or in irregular spots but occupies a uniform square area on the top of the head in a male baldness pattern are against trichotillomania.

#### A Case for Diagnosis (Premycosis Fungoides?)

Presented by MAJOR EARL A. GLICKLICH, M.C., U.S.A.

B. G., a white man aged 30, complained of an itching eruption of four years involving the groins.

The eruption first appeared on both legs. Six months later both groins became involved. Pruritus of the involved areas is a constant accompanying symptom. The patient entered the military service in 1942 and since that time has experienced recurrent episodes of the eruption, resulting in several periods of hospitalization.

Examination reveals multifiform lesions of varying sizes which are slightly indurated and erythematous and have slightly raised borders. With involution, pigmentation marks the sites of previous lesions.

Examination of the blood showed a hemoglobin content of 85 to 90 per cent, 4,500,000 erythrocytes and 5,000 to 8,000 leukocytes. The differential count was essentially normal except for an increase of eosinophils to 6 per cent. The sedimentation rate was normal. Direct smear and culture did not show fungi. A biopsy specimen was taken from the right groin. Histologic examination showed that the epithelium was thickened, with moderate intracellular edema, slight hyperkeratosis, moderate elongation and clubbing of the papillae. The basal cell layer was sharply defined. There were moderate edema of the subepithelial tissue and predominantly a perivascular infiltration of the superficial layers of the cutis by eosinophils, lymphocytes, histiocytes and a few neutrophils.

#### DISCUSSION

DR C. GUY LANE, Boston. I am interested in the suggestion about the primary stage of mycosis fungoides, and it seems to me that it is suggested by the persistent itching and some slight infiltration of the lesions in his left groin. The diagnosis can be made only by biopsy at a later date.

It would be interesting to see whether one could use roentgen irradiation as a diagnostic feature in this type of case. One could treat one or two lesions and see what change takes place after administration of 30 or 50 or 75 r. In my experience, a lesion of mycosis fungoides is apt to resolve much more rapidly than any other kind that I know of.

#### A Case for Diagnosis (Seborrheic Dermatitis?)

Presented by DR R. H. GOLDFARB, Boston.

B. L., a white Canadian housewife aged 52, presented an eruption involving the nose, lips and premaxillary areas of six years' duration. A papule first developed on the nasal septum, and it recurred intermittently until three years ago. At that time there appeared a swelling and erythematous infiltration of the nose and upper lip accompanied with scaling of the eyelids. This infiltration and edema gradually extended to involve the left cheek and ear.

Examination reveals a suffused erythema which circumscribed the nose, lips, adjacent parts of the cheek and chin. There is no pitting edema. There is slight scaling of the left ear and adjacent portion of the scalp.

Laboratory examinations showed nothing significant.

Treatment has comprised use of moist boric acid compresses, boric acid ointment and aqueous solution of zephiran chloride locally. Potassium iodide and diethylstilbestrol have been administered orally without apparent benefit.

#### DISCUSSION

DR GEORGE E. MORRIS, Boston. May I suggest the diagnosis of recurrent crsipelatus infection?

DR JACOB H. SWARTZ, Boston. May I suggest the diagnosis of chronic lymphangitis. Removal of a focus of infection may result in the clearing of the eruption.

DR GEORGE SCHWARTZ, Philadelphia. I saw this woman's eruption three or four years ago during the acute stage. She had a temperature each afternoon of 99.2 and 99.4 F. I administered sulfathiazole. While she was taking this drug, she had no recurring attacks during the time I saw her.

#### Dermatitis Venenata of the Axillas

Presented by DR FRANCIS M. THURMON, Boston.

B. B., a white girl aged 17, employed in a dental clinic, presented lesions of five months' duration in each



axilla She had used a proprietary deodorant, and afterward a papular eruption developed which burned

Examination reveals papular lesions of follicular distribution confined exclusively to the hairy portions of each axilla The cutaneous markings are exaggerated and present a slightly thickened appearance There is no evidence of infection The axillary lymph nodes are not enlarged

Treatment comprised use of moist boric acid dressings, antipruritic lotion and boric acid ointment

#### DISCUSSION

DR BERNARD APPEL, Lynn Mass It seems to me that this is Fox-Fordyce disease in an early stage I questioned the patient about lesions on the nipples and the pubis, she denied their presence I did not examine these areas The eruption is limited to the axillas In my opinion, the uniformity of the papules and their relation to the hair follicles is characteristic of this disease Apropos of this particular discussion, I should like to recall the case which I presented at a previous meeting The patient was a girl with Fox-Fordyce disease whom I had treated with roentgen therapy, to which a resistance eventually developed, with intractable pruritus The family physician referred her to Dr Lane for consultation, he agreed with my observations However the family physician referred her to Dr Eugene Traub of New York, who advised dissection of the axillas This treatment seemed radical I should be careful of the prognosis in the case presented here today

DR FRANCIS M THURMON Boston When I first saw this patient, I immediately thought of Fox-Fordyce disease If it is this disease, it is in the earliest stage I have seen That diagnosis I felt was at least questionable, since the lesions, which were confined to the axillas, almost disappeared with the use of soothing topical applications Then in order to preserve the lesions for today's presentation a slightly irritating ointment was applied

DR JOHN G DOWNING Boston My diagnosis is Fox-Fordyce Disease

DR ALFRED HOLLANDER, Springfield, Mass Should not one consider lichen simplex chronicus (Vidal) which is characterized by remissions and exacerbations? With the application of a fat ointment it becomes acutely inflamed

**Favus (Involving the Scalp, Nails and Glabrous Skin in Four Generations)** Presented by DR J H SWARTZ and DR ETHEL M ROCKWOOD, Boston

P C, aged 6, a white American schoolboy, presents an eruption of the scalp which has been present since he was 18 months old and which has been treated without success

His great grandfather had a disturbance of the scalp following an injury in childhood The grandmother since the age of 10 years has had lesions of the scalp and finger nails The mother had lesions of the scalp Other relatives have not been examined

Examination shows numerous patches throughout the scalp characterized by loss of hair, yellowish crusting and atrophy There are numerous yellowish crusts some of which are surrounded by erythematous areolas on his face A characteristic "mousy" odor emanates from the patient On the mother's scalp there is a silver-dollar-sized area consisting of central atrophic scarring and peripheral yellowish crusting The grandmother shows no active lesions of the scalp but all of her finger nail beds are involved being deformed and of yellowish white discoloration

Microscopic study of the material obtained from the involved hairs of the patient and of his mother, together with the finger nails of the grandmother, showed chiefly mycelium and also the reproductive stage of the fungus Organisms cultured from the facial lesions showed grossly the characteristics of *Trichophyton schoenleinii* The Wood filter test of the lesions of the scalp showed golden yellow fluorescence

None of these patients have been treated

#### DISCUSSION

DR JACOB H SWARTZ, Boston The lesion of the great grandfather's scalp developed when he was a young man, after an injury, according to his daughter The grandmother's lesions of the scalp and nails developed afterward The mother's lesions of the scalp appeared when she was a youngster This child has had his lesions since the age of 2, and recently lesions on the face developed The grandmother has had the lesions of the nails since shortly after the lesions of the scalp developed, when she was 10

DR ADRIAN H SCOLTEN, Portland, Maine I should like to ask Dr Swartz a question When one handles these patients with favus, is one in any danger of contracting favus?

DR JACOB H SWARTZ, Boston I have handled quite a number of them, and I frequently get enthusiastic and am not too careful So far I have not contracted favus There is a certain predisposition to this infection, otherwise one cannot explain its presence In this case the grandmother had sisters, and, as far as she knows none of them have had the infection It would be interesting to see if the child's brothers or sisters contract favus It is contagious—how and why I do not know

DR JOHN G DOWNING, Boston My most interesting experience with favus was in Morocco I was passing through the native quarter There were two little boys fighting in the street One knocked the fez off the other's head and I saw scarring with alopecia of the scalp I gave the youngster 10 cents to pose for a picture Soon we heard what sounded like a riot behind us There were about 50 children running down the street, and they all wanted their pictures taken They took their fezzes off, and all who wore fezzes had ringworm I was able to get eight Kodachrome pictures showing the various stages of favus

DR JACOB H SWARTZ, Boston What I meant was that the ordinary handling of a patient with favus does not involve high risk of contagion In certain countries and with certain populations the disease is not highly contagious In this respect, favus is similar to leprosy I recall a girl in Chelsea Mass, who had favus of the entire scalp She had brothers and sisters, and no member of the family had it except the grandmother, who had favus of the nails

DR ADRIAN H SCOLTEN, Portland Maine Is it the opinion that people in this country are more likely to contract favus than people in other countries?

DR ALFRED HOLLANDER Springfield Mass Why do American dermatologists see so few cases of favus as compared to physicians in the European countries? In Europe it is highly endemic especially in Russia After 1920 favus in children was endemic in the Rhineland On the whole the average American worker is cleaner than the average European worker and this cleanliness may be a factor explaining fewer cases here

DR FRANCESCO RONCHETTI Providence R I Those epidemics in Europe are among children Favus in adults is rare



DR ADRIAN H SCOTT, Portland, Maine May I ask what Dr Swartz is going to do with these children?

DR JACOB H SWARTZ, Boston I have not decided. In my experience the results of epilation have been disappointing, since the infection recurs and the epilation has to be repeated. I suggest a combination of roentgen epilation and ethyl iodide infiltration.

DR EDWARD A LAFRENIERE, Arlington, Mass. What roentgen dosage do you use for epilation?

DR C GUY LANE, Boston We used 280 r with 100 kilovolts and 10 milliamperes. We were using 300 r in a series of cases in which there was 100 per cent epilation. When one produces 100 per cent epilation, one never knows if the fungus is entirely destroyed or not. With 270 r we did not have quite enough epilation. I have been accustomed to consider 300 r as an erythema dose. To me, 300 r epilation dose and 1 skin unit are synonymous. That definition is not absolutely true, for the dose will vary slightly with each patient, but I feel that the epilation dose of 280 r is the safest measure.

DR WAITER T GARFIELD, Boston How many times may one safely epilate such patients with recurrent attacks?

DR C GUY LANE I think that I have treated 1 patient in this way three times. The epilation was performed after a period of six months intervened. I do not like to do that.

#### A Case for Diagnosis (Pustular Bacterid, Pustular Psoriasis?) Presented by DR W T GARFIELD, Boston

G F D, a white American man, aged 30, a clerk, has for the past nine years had a scaly eruption on his right palm. The entire palm showed a slight infiltration, white flaky scales and an erythematous base.

#### DISCUSSION

DR J HARPER BLAISDELL, Boston I am asking for the discussion of this case for the benefit of Dr Downing as well as for my own benefit. In the first place, I should like to raise the question, has the man psoriasis? Is it possible to have a single palmar lesion of psoriasis of many years' duration? The man says that he does not have dermatitis elsewhere. In the second place, if it is not psoriasis, what is it? In the third place, is it aggravated by his occupation as a freight handler? His hands are subject to trauma.

DR JOHN G DOWNING, Boston It is a question of accepting certain definite clinical entities or refusing to accept these entities. They have been described in the literature and are fairly definite in their character. As has been noted, that man had the eruption on one palm. It was sharply outlined and reflected the light, it was shiny in character and had a shiny scale and the typical brilliant red base. I first saw him as a private patient and advised him not to spend any more money, because the lesion was refractory to treatment. At that time there were typical white vesicles, which dried and became yellowish and left a dark crust or heavy scale. To my mind, that is the picture of the type of eruption which has been described by some authors as pustular psoriasis. It has also been described by George C Andrews as a recalcitrant pustular bacterid occurring on one palm or on one sole. It may be accompanied with scaly patches or with other types of eruption, and in such cases I prefer the diagnosis of pustular psoriasis. In cases in which there is no accompanying patch of psoriasis, I prefer Andrews' description.

I have had, in my own practice, cases of this type in which the patients were laborers, teachers and clerks. There is the industrial aspect—whether or not this man's work as a freight handler could be the precipitating factor of this condition. It is known that a freight handler suffers considerable trauma to the palms. Whether he were a freight handler or a school teacher, or a clerk, he might have this eruption. The most persistent eruption of the sort that I have seen was in a hotel manager. He did no manual labor. Two weeks after his tonsils were removed, the eruption disappeared. We will try sulphyridine for this man.

DR JACOB H SWARTZ, Boston I should like to suggest the diagnosis of infection with *Trichophyton rubrum*. Here is a unilateral lesion, fairly well defined, of nine years' duration. I should like to know whether cultures for *Trichophyton rubrum* have been made, since this organism could produce this very picture.

#### A Case for Diagnosis (Sarcoid, Tuberculosis Miliaris Disseminata Faciei?) Presented by DR G MARSHALL CRAWFORD, Boston

B S, a white American woman aged 77, complains of lesions on the face of eight months' duration. One year ago she had iritis of the right eye. Eleven months ago an eruption of the erythema multiforme type appeared on the dorsa of the hands. Ten months ago herpes zoster involved the left scapular region and adjacent portion of the arm. Eight months ago a red macule appeared near the right ala nasi. Shortly thereafter a row of tiny pearly nodules involved the chin. The latter grew extremely slowly, and additional nodules appeared from time to time on various parts of the face. When seen four months ago, these nodules resembled shiny pink pearls. Those on the chin were in an absolutely straight transverse line. Some had a tiny scale on top, while others were dimpled and resembled molluscum contagiosum. The lesion on the right side of the nose was an indurated plaque of bluish red color and suggested a fixed eruption. Three months ago the iritis recurred. Two weeks ago, the small nodules were observed to be darker, and a few appeared to be of an apple jelly color on diascopic examination.

A biopsy revealed a "granulomatous reaction suggesting sarcoid." Roentgenograms of the bones of the hands were normal. Roentgenograms of the chest revealed enlarged hilar nodes of the left lung, with a few dense minute nodules along the bronchi. There was some irregular enlargement of the right hilar nodes, with peribronchial fibrosis. There were a generalized irregular increase of the bronchial markings on the right and one or two pulmonary infiltrations in the upper lobe of the right lung, laterally. All the pulmonary changes were interpreted as being "possibly tuberculous, probably inactive." The hilar changes were "questionably due to early sarcoid involvement." The Hinton reaction of the blood was negative. The hemoglobin content was 85 per cent, erythrocytes numbered 5,300,000 and leukocytes 7,800. Reactions to tuberculin (old tuberculin, diluted 1:100,000 and 1:10,000) were negative. Reaction to a tuberculin patch test (Volmer) was negative.

#### DISCUSSION

DR C GUY LANE, Boston As I looked at this patient, I thought that the eruption was most probably sarcoid. I did not think that it was lupus erythematosus.

DR G MARSHALL CRAWFORD, Brookline, Mass. Clinically, I favor a diagnosis of tuberculosis miliaris faciei, and among the dermatologists with whom I have discussed the slide, it was agreed that it appears to be



11,150 white cells, with 74 per cent polymorphonuclear leukocytes, 25 per cent lymphocytes, 1 per cent myelocytes and no eosinophils. Results of subsequent examinations have been essentially the same.

The histologic reports were as follows: (1) keratinizing epithelium resting on edematous, vascular, chronically inflamed fibrous tissue, (2) vascular papilloma of the skin with hyperplasia and keratinization, and (3) the opinion of Dr F. D. Weidman given Nov. 15, 1943: "When I first looked at the photographs of H. F., I thought of so-called endothelioma capitis, but this is an epithelial tumor. Of course, a study of the sections speedily disposes of the first idea and confirms what was thought of clinically—'warts running wild'. The picture in the sections is that of a papilloma rather than of verruca vulgaris, because the hyperkeratosis which dominates the picture in verruca vulgaris is replaced here by parakeratosis and because in some of the sections, at least, the epidermis is not particularly acanthotic. Indeed, in some places it is thin and yet some long lobules extend from it. At the same time, it is not a simple papilloma, because the cells at the basement membrane are of such highly active type—carcinomatous at some places. It is strange that in these circumstances they remain so well defined by the basement membrane, I am wondering whether they would be found to be really infiltrating, cancerwise, if the biopsy specimens had extended right down to the bone. I am reminded of the cancers that occur at the base of the urinary bladder, which likewise are papillomatous at first and which produce damage by local destruction. Every now and then in general pathology one finds a contradistinction between the histologic structure and the clinical behavior of a tumor, and I feel that this case is just one more instance. The old 'adenoma malignum' of the wall of the stomach is an example. I should say that this case is one of malignant papilloma, paradoxical, though that term is."

The patient was discharged from the hospital with the condition slightly improved on Sept. 21, 1943. After various forms of treatment there were less swelling and tenderness, but a new lesion formed at the site of the biopsy wound. The patient returned on Jan. 25, 1944, for further study. There were more swelling and tenderness, and the papillomatous lesions were more pronounced.

#### DISCUSSION

DR FRANK C. COMBES: The history in this case suggests the presence of an infectious process, probably perfolliculitis abscedens et suffodiens. There are several unusual factors: first, the proliferative or vegetative lesions, not unlike those observed in dermatitis vegetans; second, the keratotic lesions, which suggest irritation of the prickle cell layer of the epidermis. In many areas there are lesions resembling a malignant papillomatosis. I think that that is the probable diagnosis.

DR CHARLES WOLF: I just saw the photograph of this patient, and it reminded me of a patient shown here many years ago, and it might be well to suggest a diagnosis of granuloma coccidioid. I suggest that studies be made in that direction.

DR ISADORE ROSEN: It is impossible to make a clinical diagnosis from one examination. Some features fit in with perfolliculitis abscedens et suffodiens, with the exception of the secondary vegetating lesions. With regard to the treatment, it might be worth while to try the use of wet dressings of gramicidin in a dilution of 1:500. If this does not give the desired result, I suggest more drastic measures, such as thorough desiccation, to be followed by the application of antiseptic solutions.

DR JACK WOLF: Malignant papilloma should not be overlooked. Papillomas of the bladder frequently become malignant. I agree with the opinion that heroic treatment should be employed.

DR GEORGE C. ANDREWS: This appears to me to be a classic case of turban tumor. Such tumors become ulcerated and infected. The histologic characteristics of turban tumors vary greatly, and treatment is a difficult problem. They are not particularly radio sensitive.

DR RUDOLPH REIDEMANN JR.: I considered all the diagnoses suggested this evening, but could not reconcile these verrucous growths with some of them. I felt that one was dealing definitely with an auto-inoculable disease. Those "boils" that developed were definitely pyogenic satellite lesions, which were opened and drained. The verrucous growths developed along the line of incision, suggesting vegetating pyoderma. It is my intention to try heroic treatment.

#### A Case for Diagnosis (Lymphoblastoma?) Presented by DR A. BENSON CANNON

J. E. C., a retired policeman, is presented from Vanderbilt Clinic, with lesions of eighteen years' duration. About eighteen years ago, he noted an enlargement in the right upper quadrant of the abdomen similar to those now present. The original lesion left a faint brownish discoloration without scarring. Shortly after the first, another large lesion appeared near the midline over the xiphoid process, and it has been present continuously for the past eighteen years. About four years ago a lesion about the size of a half-dollar appeared on the right side of the chest. This had begun to undergo spontaneous resolution when it was removed for biopsy. There is no familial history of tuberculosis or other relevant disease.

The Wassermann reaction of the blood was negative, and the urine was normal except for a faint trace of albumin. A blood count showed a hemoglobin content of 83 per cent, 4,890,000 red cells and a color index of 0.86. There were 11,100 white blood cells, with 8 per cent small leukocytes, 85 per cent neutrophils, 4 per cent band forms and 3 per cent mononuclears and a platelet count of 162,000.

Roentgenograms of the skull, chest, spine and pelvic bones showed essentially normal conditions except for a questionable fracture of the right first rib. The patient refused to submit to a sternal puncture.

The biopsy specimen was reported as showing leukoblastoma cutis circumscriptum.

#### DISCUSSION

DR FRED WISE: Despite the history of eighteen years' duration of a probable leukocytic disease, the tumors resemble nothing more closely than localized lymphoblastomas. The only alternative diagnosis that comes to my mind is a variety of dermatofibroma.

DR E. WILLIAM ABRAMOWITZ: I cannot add anything definite to the diagnosis, but I should like to be permitted to recount my experience with a physician who had a similar eruption on his back for over twenty years. He had seen several dermatologists, who made various diagnoses. My associates and I thought that he had some form of lymphoblastoma of a benign type. I later heard that he had gone to another dermatologist and received roentgen ray therapy and that the eruption subsided partially. This was about five years ago. About two weeks ago I saw him again, and he said "I still have this thing. What do you think I ought to do about it?"

DR ADOLPH ROSTENBERG: This case reminds me of the case of a patient I showed several years ago. Lymphoblastoma was suggested, the man was given

roentgen ray treatment, and the tumor disappeared in a short time. If this patient were given roentgen ray therapy and the tumor disappeared or got smaller, it would favor the diagnosis of lymphoblastoma. The tumor might recur, of course. In my patient aleukemic leukemia developed.

DR A BENSON CANNON I am of the opinion that the patient has a sarcoma and the ultimate termination will probably be fatal. While he has had the eruption for eighteen years, the lesions have become more numerous and much larger and are beginning to become a real hazard to him, although he is physically in good health. I saw a patient with similar lesions many years ago, they were diagnosed clinically and histologically as a Spiegler-Fendt type of sarcoid. Several years later the patient was admitted to the dermatologic service of the City Hospital, where he died of a metastatic sarcoma.

#### A Case for Diagnosis (Dermatitis Seborrheica, Drug Eruption Due to Phenolphthalein, Arsenical Dermatitis?) Presented by DR WILLIAM CURTH

R B, a Negro woman aged 23, is presented from Vanderbilt Clinic, with an eruption involving the forehead, ears, neck and trunk, of six months' duration.

A routine Wassermann test in May 1943 elicited a 4 plus reaction. Results of a physical examination at that time were completely normal, and the disease was classified as latent syphilis (early?). Antisyphilitic treatment was begun on June 16, 1943, with one injection of a bismuth preparation followed by 0.2 Gm of neoarsphenamine one week later. The next two injections of the neoarsphenamine (0.2 and 0.3 Gm given at weekly intervals) were followed immediately by chills and fever. Since then the patient has not received any more of the drug. She was given weekly injections of 1 cc of bismuth subsalicylate, which were continued until Sept 22, 1943. At that time an eruption appeared, at first on the forehead, gradually involving the ears and neck and finally the trunk. Since October the patient has received fourteen injections of sodium thiosulfate with only temporary effect on the dermatitis. The patient has been in the habit of taking three phenolphthalein (Ex-Lax) pills every three or four weeks regularly since the age of 19. Some pills were taken on Nov 3, 1943, and when the patient was seen three days later the dermatitis of the forehead was more irritated and showed oozing. Three pills were taken again on Jan 3, 1944, and two days later there was no change, two weeks later the areas on the face and body began to get much worse. Two roentgen ray treatments given to the face during November 1943 were without effect.

The patient now presents what appears to be a seborrheic dermatitis of the forehead, temples, ears and retroauricular folds. There are also sharply defined, coin-sized to palm-sized, round and oval scaling patches on the sternum, in the axillae, below the left breast, on the abdomen and on the entire back. Some of these patches are oozing, and others are pigmented. The arrangement of some of the lesions resembles that of pityriasis rosea.

Biopsy of an inflammatory lesion of the skin showed exfoliation of the keratin layer where there was evidence of parakeratosis. Edema of the epidermis resulted in the formation of a few small superficial vesicles. Acanthosis was pronounced, with formation of long rete pegs. The cutis was edematous and showed evidence of a chronic inflammatory reaction. The papillae were large and contained dilated capillaries. The

lesion was psoriasiform. The diagnosis was chronic psoriasiform dermatitis (seborrheic?).

The Wassermann reaction of the blood in November 1943 was 3 plus. The urine was negative for albumin and sugar.

#### DISCUSSION

DR FRANK C COMBES I think that one should be able to eliminate seborrheic dermatitis as a diagnosis, since this disease responds to roentgen ray therapy promptly. A drug eruption is the more plausible diagnosis. Although the fixed eruptions due to arsenicals and phenolphthalein not infrequently resemble each other, I favor arsenic as the most likely agent in this case.

DR ANTHONY C CIPOLLARO I think that this is another of the cases in which it is difficult to make a definite diagnosis. I believe that if these lesions were on a white person, the features of psoriasis would be more pronounced. Please note that the histologic diagnosis was chronic psoriasiform dermatitis.

#### Rosacea-Like Tuberculid (Lewandowsky) Presented by DR ANTHONY C CIPOLLARO

M J, a woman aged 25, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb 9, 1944, with an eruption on the face and a severe conjunctivitis of three and a half years' duration.

During this time the patient has been treated for a severe conjunctivitis with autogenous vaccines, vitamins and sulfonamide drugs. Thorough general examination, including that of the blood serum, tests for allergy and roentgenograms of the teeth, did not reveal any abnormalities. Diseased tonsils were removed about eight months ago. From October to December 1943, the patient was given sulfathiazole ointment for application to the eyes, without benefit.

On both cheeks, but more on the right one, and on the chin and the nose there are a number of erythematous, lentil-sized and smaller papules and pustules. The conjunctivas show pronounced injection around the cornea, and the patient suffers from photophobia.

Biopsy of a lesion on the cheek was reported as showing the features of rosacea-like tuberculid of Lewandowsky. The reaction to tuberculin was positive with a dilution of 1:1,000 but negative with a dilution of 1:10,000. A blood count revealed moderate hypochromia and an elevation of leukocytes to 13,500 white blood cells.

#### Sarcoid Presented by DR FRANK VERO

M C, a white woman aged 30, is presented from Vanderbilt Clinic, with an eruption on the face and neck of four or five months' duration.

The patient was first seen on Dec 23, 1943, complaining of an eruption of several weeks' duration which was resistant to all local treatments. There was a history of frequent colds and bronchial ailments.

On both cheeks and on the neck are a large number of solitary and grouped, reddish-brownish, papular nodular lesions, from the size of a pinpoint to that of a pinhead. In some areas an erythematous vesicular papular eruption is present. The lesions on the chin and neck remain unchanged under pressure with a glass, yellowish specks showing in some.

Tuberculin tests elicited negative reactions with dilutions of 1:1,000,000 and 1:10,000. The blood count showed a hemoglobin content of 97 per cent, 5,100,000 red cells and 8,000 white cells, with 69 per cent poly-

morphonuclear leukocytes, 28 per cent small lymphocytes and 3 per cent eosinophils

Roentgenologic examination of the chest revealed some calcific changes in both hilar regions. Roentgenologic examination of the hands showed no evidence of abnormality in the bones.

A biopsy disclosed an epidermis which was slightly edematous and in one area atrophic. The corium was the site of a diffuse chronic inflammatory reaction. Here and there within it were collections of epithelioid cells. In relation to one hair follicle these formed fairly typical tubercles which contained giant cells. The lesion was evidently a tuberculid.

The patient at first had a superimposed dermatitis venenata which cleared with soothing local medication. She has been receiving ultraviolet irradiation to the face.

#### Sarcoid, Dermatitis Venenata Presented by DR FRANK VERO

H. W., a white woman aged 21, is presented from Vanderbilt Clinic, with an eruption on the face of twenty-two months' duration.

The patient was first seen on May 18, 1943, complaining of a persistent eruption on the face which had begun about a year previously with small "pimples," slight itching and a sensation of flushing. For several years she has had anemia, for which she has received various preparations of iron, otherwise her health has been good.

Examination at that time revealed on the face (especially on the cheeks, chin and submental region) a large number of isolated and closely grouped reddish-brownish, infiltrated papular and nodular lesions, ranging from the size of a pinhead to that of a small millet seed. On diascopic pressure, the lesions showed minute yellowish discolorations. There was a considerable flush on both cheeks.

Blood counts showed the hemoglobin content to vary between 71 and 78 per cent, with 4,170,000 red cells and a color index of 1, there were 6,150 white cells, with 49 per cent polymorphonuclear leukocytes, 2 per cent staff cells, 22 per cent small lymphocytes, 24 per cent large lymphocytes and 3 per cent transitional cells. Urinalysis and roentgenologic examination of the chest revealed normal conditions. The tuberculin test elicited negative reactions with dilutions of 1:100,000 and 1:10,000.

Biopsy performed by Dr. Machacek was reported to disclose a rosacea-like tuberculid of Lewandowsky or miliarv lupoid.

The patient received local and generalized ultraviolet irradiations and injections of liver extract from May to September, when the eruption appeared to be practically cleared. She was seen again on October 21 with an acute, macular, papular and purpuric eruption on the face, which was considered to be due to the intake of anacin (a preparation of acetophenetidin with acetylsalicylic acid and caffeine). This eruption cleared in two or three weeks. She was seen again on February 16, because of an acute dermatitis of the face which was probably due to nail polish. Results of patch tests with two brands (Revlon and Miraglow) were positive. At present the dermatitis is clearing, but she still shows a few small miliarv lupoid lesions on the chin.

#### DISCUSSION OF THE PRECEDING THREE CASES

Dr. E. William Abramowitz: Dr. Cipollaro's case does not strike me as one of Lewandowsky's tuberculid. I think that this is a disease which is hard to define except when clinical and histologic appearances coincide.

I shall call Dr. Vero's case clinically a case of Lewandowsky's tuberculid and Dr. Cipollaro's case possibly an instance of sarcoid.

Dr. Anthony C. Cipollaro: It is possible that the changes in the eye and the other changes are interrelated. I think that the same tuberculous process is manifest in the eyes and in the skin.

Dr. Frank Vero: The first patient, the younger girl, I saw for the first time last May, when the eruption was of about a year's duration. While she complained of flushing of the face, I could see only small papules and at no time any pustules. Her eruption has practically cleared with ultraviolet irradiation and injections of liver extract. Some of the changes seen at present I consider to be due to a contact dermatitis caused by nail polish.

The second patient's eruption persisted for two months, and when first seen she had a superimposed dermatitis venenata from various medicines.

I believe that the two eruptions belong in the group of miliarv sarcoid. Tuberculin tests elicited negative reactions in both patients, whereas persons with rosacea-like tuberculid, according to Sulzberger, Wile and others, are usually hyperallergic to tuberculin, even in high dilutions.

#### Eruption Due to Sulfathiazole Presented by DR E. WILLIAM ABRAMOWITZ

A. de A., a girl aged 17, came to the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Feb. 21, 1944, with a generalized eruption of about two months' duration.

About Christmas 1943, the patient had impetigo of the face, for which a physician prescribed a 5 per cent sulfathiazole ointment. When after a few days the eruption became worse, the physician prescribed in addition sulfathiazole tablets to be taken internally, 1 Gm. every four hours. After seven days of this medication, the eruption was worse and the patient complained of sleepiness. The oral administration of sulfathiazole was discontinued, but the use of sulfathiazole ointment was continued to be applied at the advice of the nurse. After another physician recommended discontinuation of the use of sulfathiazole ointment, the eruption began to improve.

There is an erythematous, crusted, scaly eruption, in some areas oozing, on the face, neck, chest, forearms and thighs. The patient complains of moderate pruritus.

The urinalysis gave normal results.

#### DISCUSSION

Dr. E. William Abramowitz: Judging from experience, I should say that this type of eruption continues to spread long after use of the drug (usually externally) is discontinued, and it is extremely resistant to treatment. It assumes the aspect of an infectious eczematoid dermatitis. It is not unusual for an eruption of this kind to last four to six months or even more. It is the duty of dermatologists to warn general practitioners against using this ointment, especially when other measures can be just as effective.

#### Keratosis Palmaris et Plantaris Presented by DR RICHARD J. KEELY

S. O., a white housewife aged 60, was first seen at Vanderbilt Clinic on Jan. 31, 1944. At that time she complained of thickening, scaling and fissuring of the palms and soles of twelve months' duration. The general health was good, the blood count normal and





port a so-called bullous Darier's disease. This disease has a characteristic picture, and the patient presents all the features of it. This diagnosis is not corroborated clinically, but microscopically that is the picture.

DR E. WILLIAM ABRAMOWITZ: I recall a patient with an eruption of the same type, who was presented at the Brooklyn Dermatological Society at one of the early meetings. There was considerable discussion at that time as to whether the patient had the bullous type of lupus erythematosus or pemphigus. His eruption later developed into lupus erythematosus of the face. I do not think that this lesion is an artefact.

DR ANTHONY C. CIPOLLARO: No one can make an unequivocal clinical diagnosis in this case. I have not the least idea what the disease is, but, since the histologic picture suggests the possibility of bullous dyskeratosis, a diagnosis of Bowen's disease might be made. The treatments which this patient has received are usually effective for the other diseases mentioned. I suggest treating one small area with desiccation and curettage.

DR WILBERT SACHS: There is no dyskeratosis in this lesion. This is a so-called bullous Darier's disease. The cells are large, the nuclei are well stained and round, and the prickles are gone. There is normal epithelium above the areas of so-called dyskeratosis. These cells are ballooned, not dyskeratotic.

DR MAX SCHEER: I cannot get away from Dr Chargin's first impression, that the lesion is an artefact, self-induced. The patient says that he is a nervous, apprehensive person, has had an impulse to rub and scratch and admits that he traumatized and continues to traumatize the lesions. My impression is that the eruption is an artificially produced dermatitis, and I suggest that Dr Chargin refer the patient to a psychiatrist.

#### Riehl's Melanosis Presented by DR HELEN CURTH

I de B., a Negro woman aged 39, is presented from Vanderbilt Clinic with a pigmentation of the face of six months' duration.

The patient was well until last summer. She has always freely used Noxzema, Pond's vanishing and cold creams and petrolatum as a powder base. There was no undue exposure to the sun, as the patient knew that her skin would peel after such exposure. In August 1943, her face began to become darker. She continued to use the creams until January 1944, when she was first seen in the department of dermatology at the Vanderbilt Clinic. Bleaching creams with hydrogen peroxide and ammonia did not improve the discoloration.

There is reticular hyperpigmentation on the bridge of the nose and on the forehead, with confluent hyperpigmentation on the cheeks, upper lip and chin. (The patient thinks that lately this confluence has been interrupted in places by normal skin.) There is a mild papular rash on the right side of the chin. Further examination reveals pigmented spots on the buccal mucosa, mild keratosis pilaris of the arms and several keloids.

The Wassermann and Kahn reactions of the blood were negative.

Biopsy disclosed hyperkeratosis and a slight acanthosis of the edematous epidermis. The corium showed a striking perivascular infiltration of small mononuclear cells. Just beneath the epidermis were numerous chromatophores. The lesion was a melanodermatitis and was probably the so-called melanodermatitis of Riehl.

#### DISCUSSION

DR CHARLES WOLF: The patient is exposed to heat and employs cosmetics, although she disclaims exposure to the sun directly, nevertheless hers is a sharply demarcated, hyperpigmented eruption without any inflammatory clinical manifestations. Riehl's melanosis is about the best diagnosis one can offer at present.

DR FRED WISE: I think the diagnosis is acceptable under that name. I should like to call attention to a booklet (Pierini, L. E. *Dermatosis pigmentarias de la cara y del cuello*. Imprenta de Alfredo Frascoli, Buenos Aires, Argentina, 1941) published in Argentina, containing numerous photographs of dark-complexioned natives, not Negroes, in whom this type of eruption is said to be extremely common after prolonged use of cosmetic creams.

DR HELEN CURTH: Riehl's melanosis was first described in Europe. It occurs mostly in dark-skinned women under certain conditions. I believe that the histologic changes in this patient are rather characteristic of this disease. There is an increase of the chromatophores, and there is evidence of an inflammatory process in the cutis. Clinically, there are no signs of an inflammatory process.

#### Systematized Epidermal Nevus Presented by DR HELEN CURTH

C. K., a Jewish girl aged 13, is presented from Vanderbilt Clinic, with generalized dark streaks on the skin which began to appear at 6 months of age.

The patient is the third of four children, and none of the others are similarly affected. There is no consanguinity of the parents and no history of cancer in antecedents.

When the patient was first seen in the Vanderbilt Clinic, in 1937, the eruption was almost as widespread as it is now. Elevated hyperkeratotic thickened brownish to blackish skin is present symmetrically on the neck, in both axillas, on the flexor side of the arms, in the cubital areas, on the extensor surface of the elbows and forearms, on the lower sides of the chest, on the flanks, in the inguinal areas (assuming a streak-like appearance from the buttocks to the flexor side of the knees) and extensively on the extensor surface of the feet. There is mild redness of the skin in the axillas. Last Christmas, blisters on the soles were observed which may have been impetigo.

Results of a general examination and analysis of the blood have been repeatedly normal.

Biopsy of specimens from the axillas, taken in June 1937, revealed focal papillary proliferations of the epidermis with pronounced hyperkeratosis and acanthosis. The epidermal cells disclosed a spongy degeneration, particularly among cells which contained keratohyalin. There were no abnormal deposits of melanin. This substance seemed to be depleted rather than increased in quantity. The diagnosis was epidermal linear nevus.

Biopsy from the shoulder in December 1943 disclosed areas of loose hyperkeratosis and some parakeratosis. The epidermis at these sites showed evidence of acanthosis and a peculiar spongiosis of the epidermal cells, as well as pronounced disturbance of the keratohyalin. There was also evidence of dyskeratosis in that many of the shrunken epithelial cells were highly eosinophilic. The lesion was interpreted as an epidermal nevus with changes suggesting epidermodysplasia verruciformis.

Treatment has consisted of about forty-six injections of liver extract, roentgen irradiation, exposure to the sun, vitamin A in doses of 50,000 U. S. P. units for nine

weeks and 100,000 units later with local applications of salicylic acid and chrysarobin. While the patient's mother has thought that there was sometimes definite improvement following the use of these medicaments, I was never convinced of this.

#### DISCUSSION

DR HELIX CURTH. Some but not all, of the features of this verruciform nevus seemed to fit into the diagnosis of acanthosis nigricans, Darier's disease or erythroderma ichthyosiforme congenitale. I thought I

had a lead when Dr Machacck observed vacuolation of the epidermal cells and changes of the keratohyalin which he considered characteristic of epidermodysplasia verruciformis. Weisman and Montgomery (ARCH DERMAT & SYPH 45 259 [Feb] 1942) described a case of the same type of nevus in a boy of 11. I believe that the photographs of that patient and the patient presented tonight could be interchanged. This case is again proof that epidermodysplasia verruciformis is an epithelial nevus.

## Book Reviews

**Manual of Clinical Mycology** Military Medical Manuals Prepared under the Auspices of the Division of Medical Sciences, National Research Council. Price, \$3.50. Pp 348 with 148 illustrations. Philadelphia: W. B. Saunders Company, 1944.

The newest addition to the study of mycology, in 1944, is a Manual of Clinical Mycology, one of a series of Military Medical Manuals, "developed in order to furnish the medical departments of the United States Army and Navy with compact presentations of necessary information in the field of military medicine." It is the result of cooperative work of the following authors: Norman F. Conant, Donald Stover Martin, David Tillerson Smith, Roger Denio Baker and Jasper Lamar Callaway. The Manual consists of twenty-five chapters and an appendix. The diseases discussed are actinomycosis, blastomycosis, coccidioidomycosis, geotrichosis, chromoblastomycosis, cryptococcosis, moniliasis, histoplasmosis, sporotrichosis, maduromycosis, aspergillosis, penicilliosis, mucormycosis, rhinosporidiosis, the dermatomycoses, piedra, trichomycosis axillaris, tinea versicolor, erythrasma and otomycosis. A special chapter is devoted to the immunology of the dermatomycoses, cutaneous and serologic tests, dermatophytids and desensitization. Another chapter deals with the mycology of the dermatomycoses, the classification of fungi and their morphologic characteristics in lesions and in cultures. The fundamental of elementary mycology, the general classification of fungi and the various forms of myceliums and spores are discussed in a separate chapter. The last chapter is devoted to the description of thirty common contaminants. In the appendix are given mycologic laboratory techniques, pathologic and immunologic methods, methods of examination under Wood's light and a formulary of useful prescriptions. The list of references in each chapter includes publications appearing up to 1944. The illustrations are a major asset of the book. There are numerous and instructive clinical photographs, reproductions of roentgenograms of lungs and bones, photomicrographs of fungi in the lesions observed on direct examination or in sections, biopsy or autopsy material and pictures of gross and microscopic morphologic structures of cultures.

The book has been written for general medical practitioners. Three fourths of it is devoted to the discussion of mycotic diseases which are or may become systemic. About one fourth is given to the discussion of the dermatomycoses. The discussion of the systemic mycoses is remarkably complete for a manual of this size, but the description of the dermatomycoses is somewhat too brief and may not satisfy a dermatologist. The expressions "Trichophyton unguum" (page 217)

and "Trichophyton corporis" (page 221) should be replaced by the terms "trichophytosis unguum" and "trichophytosis corporis." In the description of tinea capitis it is stated (page 230) that hair is loosened and can be epilated readily. Unfortunately, this is not quite so. If it were so easy to epilate hair manually, then it would be easy to cure tinea capitis by manual epilation without the use of roentgen rays. In cases of tinea capitis, however, only a few hairs can be epilated, that is, removed entirely from their follicles by the manual method. As a rule attempts at manual epilation effect only breaking of the hair, leaving a good part of it in the follicle, that is why the disease continues. The statement that alopecia usually develops in the infected area is somewhat misleading. In cases of ordinary (noninflammatory) tinea capitis there is no true alopecia. The hairs are not absent but are merely broken off short.

The reviewer cannot agree with the statement that favus may be produced by *Trichophyton violaceum* or *Microsporon gypseum*. *T. violaceum* does not cause favus. Lesions produced by this fungus on the scalp have all the characteristics of ringworm and not of favus, namely, short, broken or "black dot" hairs but with no scutula, no atrophy, no alopecia and no "mousy odor," and there is a tendency toward spontaneous cure at the age of puberty. The microscopic morphologic structure of *T. violaceum* in the hair is that of a typical trichophyton, usually of the endothrix type. The statement that *M. gypseum* may cause favus is, in this reviewer's opinion, a misunderstanding. If a fungus is a true microsporon, then it will cause ringworm but not favus, and the appearance of the parasite in the hair will be that of a microsporon. All this confusion regarding the cause of favus is due to the classification of the dermatophytes in the Manual, a classification which eliminates the genus *Achorion* and redistributes several species formerly placed in this genus among trichophytons and microsporon. This is done in order to simplify the matter. In the reviewer's opinion this new classification complicates rather than simplifies it. The earlier classification worked out by Sabouraud and followed by many contemporary mycologists and dermatologists established the genus *Achorion* and referred to it all fungi capable of producing favic scutula in the human or animal skin, regardless of the gross and microscopic morphology of cultures. According to Sabouraud's classification, favus is an independent clinical and etiologic entity different from ringworm and is due (with very rare exceptions) to the fungus *Achorion schonleini*. Other fungi placed in the genera *Trichophyton* and *Microsporon* have nothing to do with favus. This conception seems cor-

rect, simple and easy to understand. The matter becomes much more complicated if one assumes (as is done in the Manual) that ringworm and favus are only different clinical manifestations which may be produced by the same fungus and that favus, also, may be caused by *T. violaceum* or by *M. gypseum*. The assumption is, in other words, that the same fungus (for instance, *T. violaceum*) in some cases will produce a typical ringworm of the scalp and in other cases will cause a typical favus with scutula. With this conception the reviewer cannot agree. It would also be advisable to mention in the description of favus that scutula are not simple crusts but masses of fungi in almost pure culture, a pathognomonic feature of favus not present in any other disease of the skin. It would be useful to stress that scutula constitute the best material for a microscopic diagnosis of favus, because the picture of fungi in a scutulum is even more characteristic of favus than the appearance of fungi in a hair.

The description of the appearance of *Trichophyton* and *Microsporon* in the hair (pages 246 and 247) is somewhat incomplete and may confuse a laboratory worker. It is stated that a *Trichophyton* endothrix shows parallel rows of spores inside the hair, a *Trichophyton* ectothrix shows parallel rows of spores outside the hair and a *Microsporon* forms a mass of spores around the hair. This is the truth but not the whole truth. It should be added that *T. endothrix* may show a mass of spores without linear disposition inside the hair, which looks like a sack full of potatoes (a common picture for *T. violaceum*). *T. ectothrix* is present not only outside but also inside the hair, and the spores may be arranged not only in chains but also irregularly. The *Microsporon* gives not only a mass of spores around the hair but filaments inside the hair.

It is stated (page 253) that the species known under the names *Trichophyton album*, *Trichophyton discoides* and *Trichophyton ochraceum* are identical with the fungus *Achorion schonleini* of favus. The question was investigated by Sabouraud almost half a century ago, and he concluded that they are not identical. He placed the three species in the genus *trichophyton* under a group name, *Trichophyton faviforme* that is, with cultures resembling the fungus of favus but not identical with it. Several reasons impelled Sabouraud to establish this differentiation. Formation of scutula is usual and a most characteristic feature of favus, in spite of the fact that favus may produce lesions resembling trichophytosis (favus herpeticus). Cultures obtained from favic scutula are not of *T. faviforme* type but of *Achorion schonleini* type. Lesions caused by *T. faviforme* on human and animal skin have all the features of ringworm and not of favus, and there are no scutula. The microscopic picture of *T. faviforme* in a hair differs from the picture seen in favus and is of the type *T. ectothrix*.

On page 319 there is a formula for the preparation of Sabouraud's dextrose agar medium, giving the amount of agar as 3.5 per cent and advising the use of distilled water. The original formula suggested by Sabouraud contained only 1.8 per cent agar, and distilled water was not required. Plain tap water was found to give excellent results.

In the discussion of pleomorphic degeneration (page 249) it would be useful to mention that this can be prevented by making a transfer of the isolated strain on Sabouraud's "conservation" medium, consisting of 3 per cent of peptone and 1.8 per cent agar in plain water without carbohydrates.

**Essentials of Allergy** By I. C. O. Price, \$5 Pp 381, with 42 illustrations in black and white and 1 plate in full color Philadelphia J. B. Lippincott Company, 1945

In this compact volume the author has given a large amount of information, which is concisely stated and easily understood. The subject matter is presented in outline form and includes chapters on anaphylaxis, allergy, diagnosis and treatment of allergy, pollen allergy, bronchial asthma, nasal allergy, cutaneous allergy, serum allergy, drug allergy and bacterial allergy. Selective bibliographies supplement each chapter.

Some chapters are followed with case reports, which illustrate essential practical considerations and emphasize diagnostic and therapeutic methods. A goodly number of photographs and tables are included, which greatly enhance the value of the book.

Useful diets free from egg, wheat and milk are given and numerous recipes which do not contain wheat and egg.

A weak section of the book is the chapter on cutaneous allergy. Not only is the subject poorly presented and inadequately covered, even for a book of this size, but many of the opinions expressed are vague and will not meet with the approval of most dermatologists. For example, in the discussion of pathology and immunology of contact dermatitis (page 218), the following statement appears: "It should be pointed out that the lesion of contact dermatitis may be reproduced either by patch test (that is, by exposing the skin to the causative substance), or (as in the case of poison ivy and some other agents) by ingestion."

The lesion produced as a result of contact in these individuals is a vesicle."

Contact dermatitis does not produce only one type of lesion (vesicle), nor do positive reactions to patch tests always reproduce clinical lesions. If by "ingestion" the author meant to indicate that contact with an allergen may also be from within, why should he select poison ivy as an illustration?

The last paragraph on page 219 begins with more or less correct observations but ends in meaningless phraseology: "Those substances which are soluble in the oil of the skin, or others which can penetrate the horny layer of the epidermis and have an affinity for the epidermal cells, will more readily produce contact dermatitis. For this reason various chemicals and dyes and the oily fraction of certain plants are good contactants. In this group are found instances of allergy to vegetable and plant oils, such as poison ivy and ragweed, occupational contact dermatitis due to metals and chemicals, similar lesions due to contact with furs, dyes, leathers, cosmetics and drugs. The condition is characterized by intense pruritus, which leads to scratching and skin trauma."

On page 231 the following statement appears: "It occasionally becomes necessary to differentiate an allergic dermatosis from such conditions as scabies or seborrheic dermatitis or insect bites. Frequently, one of these two skin conditions is found together with some form of allergic dermatosis. In seborrheic dermatitis one does not elicit any of the criteria for allergic diagnosis. The distribution of the lesion is about the hairy portion of the skin. The skin is oily and acne is present. The lesion is pustular." Most of these statements are dermatologically incorrect.

Many other objections could be cited, but for the sake of space the reviewer will stop at this point and respectfully suggest that in the next edition the author collaborate with a dermatologist.

All in all, the book deserves circulation among general practitioners, for whom it is intended.

O. C. G. Medical College

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